EXHIBIT C

TVT-SECUR EXPORT REPORT OF RALPH ZIPPER, MD FPMRS

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Background And Qualifications

I am board certified in Female Pelvic Medicine and Reconstructive Surgery (FPMRS) and Obstetrics/Gynecology. I received my medical degree in 1992 from The Mount Sinai School of Medicine of the City University of New York. In 1996, I completed my fellowship in the field of Obstetrics/Gynecology at the John Hopkins Hospital, Department of Gynecology and Obstetrics, Baltimore, Maryland. My practice of medicine has been dedicated to Urogynecology, FPMRS, for eighteen years. I am the president and director of Zipper Urogynecology Associates (ZUA). Over the last ten years I have trained over one thousand urologists and gynecologists in the techniques of prolapse and incontinence surgery.

Over the last 18 years I have performed thousands of incontinence and prolapse procedures, including native tissue repairs, allograft repairs, xenograft repairs and

synthetic mesh repairs. I have experience implanting and explanting multiple constructions of polypropylene mesh implanted by numerous methods including by way of example Gynemesh, NovaSilk, MiniMesh, Pelvitex, Prolift, Avaulta, Perigee, Apogee, Pinnacle, as well as retropubic, suprapubic, transobturator, and single incision sling products of Bard, Ethicon, American Medical Systems, and Boston Scientific. I was the first surgeon in the United States to perform a single incision sling and worked for several years, with my engineer to solve its efficacy and complication problems. I stopped using pelvic organ prolapse repair kits (POP kits) approximately eight years ago as I became increasingly concerned that these POP kits, including the PROLIFT kits, were associated with an unacceptable high rate of complications due to their armed designs and the large polypropylene inoculum. Likewise and for similar reasons, I stopped using single incision slings approximately seven years ago and transobturator slings about four years ago. My concerns were validated by my own clinical experience, the experience of my colleagues, the medical community as a whole, and further confirmed by both the FDA and the medical and scientific literature.

In addition to my role as a urogynecologist at Zipper Urogynecology Associates (ZUA), I am also currently serving as the President of Zipper Urogynecology Associates, the CEO of Uroshape, LLC (Develops laser technology for pelvic pain), the CEO of BioFuse Medical Technologies, Inc. (Develops proprietary bipolar RF technology for use in FMPRS and general surgery), and am working actively as a corporate consultant to companies in both the device and pharmaceutical spaces. I have authored fifteen relevant patent applications and have been issued multiple patents relevant to the field of pelvic medicine and reconstructive surgery.

Between the years of 1998 and 2008, I served as the Keynote Speaker on Pelvic Reconstruction Surgery at the annual National Sales Meeting for both C.R. Bard and American Medical Systems. I lectured physicians at national meetings on prolapse and incontinence surgery, for both C.R. Bard and Coloplast. Additionally, Coloplast commissioned myself and Dr. Neeraj Kohli to author an abstract on the NovaSilk mesh product. This paper was presented at the International Urogynecological Association (IUGA) meeting in or about 2008. Additionally, I served as a product development consultant to Boston Scientific. I met with Coloplast engineers and patent counsel to discuss my methods and devices for the treatment of stress urinary incontinence and pelvic organ prolapse. I served as a physician trainer for C.R. Bard for many years. During these years over three hundred physicians from across the United States were sent by C.R. Bard to watch me use the C.R. Bard xenograft prolapse product and incontinence products. During this time C.R. Bard also sought my opinion on product development including the licensing and or purchasing of mesh products from inventors and manufacturers.

As a private independent consultant, I have worked closely with engineers to develop devices including slings for the treatment of stress urinary incontinence, methods for the treatment of stress urinary incontinence, and mesh products and methods for the treatment of pelvic organ prolapse, many of which were subsequently deployed and sold by foreign and U.S. medical device companies. In this same role, I worked extensively to develop instructional materials and marketing materials for prolapse mesh and incontinence products.

I am familiar with the type of information that should be communicated to surgeons so that surgeons can make reasonable informed choices when considering medical products. I have read and am familiar with the IFU's, sales and marketing materials, and physician training materials, including videos for mesh products. I have also reviewed the TVT-Secur IFU and other IFUs for other transvaginal mesh products that I have implanted in my practice of FPMRS

As part of my practice, I routinely treat mesh complications. I have revised and/or explanted hundreds of mesh devices, including but not limited to TVT, TVT-SECUR, TVT-O, Align, Obtryx, PROLIFT, and AVUALTA, from women experiencing chronic mesh complications including but not limited to, infections, erosions/extrusions, urinary dysfunction, deformity and pain from contracted mesh, chronic dyspareunia and chronic pelvic pain. As part of my practice as a Urogynecologist, I keep current on the peer-reviewed publications concerning mesh devices and associated complications and am keenly familiar with the risks and complications associated with mesh procedures and devices, including those associated with TVT-SECUR.

A copy of my current curriculum vitae is attached as Appendix A, more fully detailing my training, background, and publications. I have also attached as Appendix B, a list of the materials I relied upon in formulating my opinions. Appendix C is a list of my testimony during the last four years.

I reserve the right to supplement my report. I also reserve the right to use various demonstrative exhibits at trial to educate the jury on TVT-SECUR device and methods and its impact on the female pelvic anatomy.

Method of Opinion

In formulating my expert opinions, I apply my knowledge, training, and experience as a physician, medical device company senior executive, and trainer of physicians, as well as my knowledge of the peer reviewed medical and scientific literature, my review of the available relevant medical and scientific literature, regulatory documents and databases, internal corporate documents, corporate and expert testimony, prior art, samples of products, and opposing opinions. All opinions rendered herein are to a reasonable degree of medical, scientific and professional certainty. As discovery is ongoing, I reserve the right to amend my opinion as further information becomes available.

Urinary Incontinence

The International Continence Society (ICS) and the International Urogynecology Association (IUGA) define urinary incontinence as the complaint of involuntary loss of urine. Approximately 30% of women age 30-60 suffer from urinary incontinence. The two most common types of urinary incontinence are Stress Urinary Incontinence (SUI) and Urgency Urinary Incontinence (UUI). As many as half of all women with urinary incontinence suffer from the SUI.

The Cause of SUI

The underlying pathology of SUI is in many ways similar to that of pelvic organ prolapse. Most commonly, damage to the supporting tissues of the pelvis such as the connective tissue around the urethra and the muscles of the pelvic floor leads to descent of the urethra. This descent is most evident during exertion. As intra-abdominal pressure increases, this pressure is transmitted to the bladder, encouraging the movement of urine

into the urethra. The descending urethra is unable to stay closed. This results in urinary incontinence. There are different theories as to why this loss of urethral support results in a failure of the continence mechanism.

One historical theory is that of differential pressure transmission. As the urethral moves down and out of the pelvis it is not subject to the increased intra-abdominal pressure transmitted to the bladder. Another theory is that the normal intact pelvic floor serves as a backboard, compressing the urethra as it tries to descend during exertion. Additionally, the normal resting urethra is maintained in a closed position. This closure is the result of both intact "sphincter" muscles and a healthy, plump, lining. Damage to the sphincter mechanism and or scaring of the periurethral tissue can result in a urethra that is open at rest. This type of SUI is called Intrinsic Sphincter Deficiency (ISD). Many women with SUI have a combination of hypermobility (loss of urethral support) and ISD.

The Treatment of SUI

Stress urinary incontinence may be treated non-surgically or surgically. Non-surgical treatments include pelvic floor muscle training (PFMT) and weight loss. The highest level of medical evidence is the systematic review of randomized controlled trials (RCT). The Cochrane Collaboration is a not-for-profit international network of health practitioners and researches that promote evidence based medicine by performing high quality systematic reviews of predominantly randomized controlled trials. The Cochrane reviews are internationally recognized as the highest standard of evidence-based health care.

In May of 2014, the Cochrane Collaboration published its systematic on Pelvic Floor Muscle Training. They found that 55% of women undergoing PFMT reported a

cure.[1] The association between obesity and SUI is well established. At least one RCT of weight loss in overweight and obese women has demonstrated it to be as effective as other non-surgical SUI treatments.[2]

Women not responding to non-surgical intervention or opting not to attempt such conservative management may choose to have a urethral bulking agent implantation or undergo surgery.

Bulking Agent Implantation

Synthetic or natural materials may be injected into the wall of the urethra. The injected implant material causes the walls of the urethra to coapt, come together. When the implant is optimally situated, the coaptation is sufficient to resist moderate pressure increases but is easily overcome by the normal voiding mechanism. Although bulking agent procedures have been performed for decades, there is a paucity of RCTs. Nonetheless, the available data consistently shows significant improvement in SUI symptoms with minimal complications.

This five-minute procedure may be performed in the physician's office with or without local anesthesia. Complications are mild and include a 0-12% risk of temporary urinary retention and or urinary tract infection, and less than one percent risk of hematoma. The majority of data demonstrates 18 month cure rates ranging from 50-

[1] Dumoulin C, Hay-Smith EC, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment for urinary incontinence in women. The Cochrane Collaboration. May 14, 2014

[2] Subak LL1, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS. Weight loss: a novel and effective treatment for urinary incontinence. J Urol. 2005 Jul;174(1):190-5.

75%.[3] Efficacy decreases over time and many patients will be significantly symptomatic within 18 months.

Although results are short lived and cure rates are lower than surgical intervention, urethral bulking agent implantation is a 5-minute, office procedure with minimal associated complications. Originally it was thought that bulking agent implantation was only effective in the treatment of the type of SUI known as ISD, there is now evidence that it is equally effective in treating patients with SUI and hypermobility of the urethra.[4]

The Most Common Surgeries For Sui

Retropublic Colpourethropexy

These surgeries, The Marshall-Marchetti-Krantz (MMK) and Burch Procedures, involve the suturing of the patients peri-urethral tissue to the periosteum of the public bone or a strong ligament approximating the pubic bone, coopers ligament. These surgeries are typically performed through an incision in the lower abdomen just above the pubic bone.

Autolgous Sling Surgery

These surgeries, first described in the early 1900s, involve the creation of a sling beneath the urethra. In order to place the sling, one incision is made in the lower abdomen, just above the pubic bone, and a second incision is made inside the vagina. The sling is typically fashioned from strong tissue known as fascia that is harvested through

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[3] Interventional procedures overview of intramural urethral bulking procedures for stress urinary incontinence in women. NICE. National Institute for Health and Care Excellence, Dept of Health, U.K., Lindsey A Kerr. Bulking Agents in the Treatment of Stress Urinary Incontinence: History, Outcomes, Patient Populations, and Reimbursement Profile. Rev Urol. 2005; 7(Suppl 1): S3–S11.

[4] Herschorn S, Radomski SB, Steele DJ. Early experience with intraurethral collagen injection for urinary incontinence. J Urol. 1992;148:1797–1800. ,Herschorn S, Radomski SB. Collagen injections for genuine stress urinary incontinence: patient selection and durability. Int Urogynecol J. 1997;8:18–24.,Monga AK, Robinson D, Stanton SL. Periurethral collagen injections for genuine stress incontinence: a two- year follow-up. Br J Urol. 1995;76:156–160. ,Steele AC, Kohli N, Karram MM. Periurethral collagen injection for stress incontinence with and without urethral hypermobility. Obstet Gynecol. 2000;95:327–331.

either a small incision in the patient's leg or through the same abdominal incision used for sling placement. The surgeon places the sling through the vaginal incision and pulls each end up through the vaginal incision. The surgeon then sutures the sling to the rectus fascia, strong connective tissue overlying the main muscles of the abdomen.

Allograft And Xenograft Sling Surgeries

These slings are fashioned from cadaveric or animal tissue. The surgery is otherwise similar to the Autologous Sling Surgery.

Midurethral Synthetic Sling Surgery (MUS)

As it is known and performed today, this surgery involved the placement of a synthetic sling fashioned from monofilament knitted polypropylene mesh under the mid-urethra. This surgery, a much more recent innovation that the retropubic colpurethropexy and autologous sling, was first described in the 1990s by Petros and Ulmsten. This sling surgery is performed through a small vaginal incision and two additional small, fingernail sized incisions, just above the pubic bone or right and left of the labia.

The original method of this MUS surgery was commercialized in the form of a kit, TVT, by Ethicon in 1998. The surgical planes coursed by this sling were and are identical to those coursed by the original sling surgeries performed for over 100 years. In 2001 Delorme described a new method of MUS placement, The Transobuturator Method. This method, commercialized first by Mentor in 2003, is quite different than both the traditional sling surgery and the TVT surgery. Although the sling is placed beneath the mid-urethra, it oes not terminate at the rectus fascia. The sling is carried through the obturator fascias and muscle and terminates the adductor space of the groin.

The Evolution Of The MUS

Slings surgeries were first described in the early 19th century. Until 90 years later, slings were performed at the level of the proximal urethra and almost exclusively with autologous fascia. In 1995 Ulmsten and Petros described a less invasive method for sling surgery. This surgery involved the placement of a synthetic sling, through small incisions. The sling differed then the traditional sling surgery in two ways. The sling rested at the level of the mid-urethra rather than proximal urethra and the sling would terminate on but not be sutured to the rectus fascia. It would scar in place. The former feature could result in a lower incidence of postoperative lower urinary tract voiding symptoms and storage symptoms (less trouble urinating and less urgency and frequency).

The later feature made the procedure less invasive. The surgeon no longer had to make a big incision to suture the sling to the rectus fascia. With the exception of these two novel features, the surgery remained essentially unchanged from traditional sling surgery. The path of the sling remained consistent with the last 90 years of teaching and urologic practice. No novel anatomic planes were traversed. Preliminary data was very encouraging. Papers published by Ulmsten and Petros in 1995 and 1996 reported cure rates at least as good as those of traditional slings and colpourethropexy. That same reports describes a lower incidence of post-operative voiding and storage symptoms than would be expected from traditional surgeries.[5]

In 1998, Ethicon initiated the U.S. commercialization of the MUS method of Ulmsten and Petros. The product was called TVT. TVT was marketed as a kit that contained a macroporous monofilament polypropylene mesh sling as well as needles used

[5] Petros PE: The intravaginal slingoplasty operation, a minimally invasive technique for cure of urinary incontinence in the female. Aust NZ J Obstet Gynecol 36: 453– 461, 1999.,Ulmsten U, and Petros P: Intravaginal slingoplasty (IVS): an ambulatory surgical procedure for the treatment of female urinary incontinence. Scand J Urol Nephrol 29: 75– 82, 1995.

to insert the sling. With the exception of the fact that the sling was inserted from the vagina up rather than the being pulled up from the suprapubic incision, this method was quite similar to that of traditional sling surgery. Gynecologists and Urologists who were residency trained in traditional sling surgeries were quite familiar with the anatomy of both the retropubic and the vaginal spaces. They possessed the essential know-how to both implant the TVT and manage complications.

In 2001 and 2002, American Medical Systems and C.R. Bard introduced their versions of TVT, SPARC and Uretex. Similar to TVT, these sling kits were marketed as macroporous monofilament polypropylene mesh and needles for insertion for the treatment of SUI. Unlike TVT, the SPARC and Uretex offered a "from above-to-below" insertion method. This method bared even greater similarity to the traditional autologous sling method. Other companies would follow suite including Boston Scientific with two MUS kits, The Advantage System (bottom up like TVT) the Lynx System (top down like SPARC). The ease and time savings associated with the MUS (compared to traditional incontinence surgery) combined with an efficacy comparable to or greater than traditional incontinence surgeries, led to rapid adoption.

The Birth Of The Transobturator Sling (TOT)

In 2000, Emmanuel Delorme filed an international patent application under the Patent Cooperation Treaty (PCT) for a novel method of MUS placement, the transobturator method (TOT). This method traversed anatomic planes unknown to urologists and gynecologists. Rather than piercing and securing to the rectus fascia of the abdomen, Delorme described a method of penetrating the muscles and fascia of the groin

and legs. He proposed that this method would negate the risk of bladder perforation and obviates the need for the surgeon to perform a cystoscopy.

The TOT kits enjoyed early marketing success. Thousands of gynecologists had been precluded from the TVT type slings as they were not residency trained in cystoscopy. As the TOT procedure could be performed without cystoscopy, many new adopters were brought on board. By the end of 2004 thousands of women had undergone TOT procedures.

A Comparison of Incontinence Surgeries

Transobturator vs Retropubic Midurethral Slings

In 2010, the largest randomized controlled trial comparing the TOT method to the predecessor Retropubic polypropylene mesh midurethral sling.[6] This study, as well as the preceding and proceeding systematic review of the Cochrane Group failed to demonstrate superior efficacy of one method over the other.[7] *The 2015 Cochrane systematic review of the literature, including 81 clinical trials reported that "These trials showed that over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either operation, for up to five years after surgery. We found this to be the case irrespective of the tapes used and the route of tape insertion*". The TOT approach is associated with a higher incidence of groin pain, lower extremity neurologic symptoms and a lower incidence of bladder perforation.

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[6] Richter, H.E., et al., Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med, 2010. 362(22): p. 2066-76.

[7] Ogah J1, Cody JD, L.Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4), Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2015, Issue 7.

Midurethral Slings vs. Traditional Slings vs. Colpourethropexy

In 2009 the Cochrane Collaborative published its systematic review of 62 clinical trials involving MUS. This review compared synthetic MUS procedures to both traditional sling surgeries (autologous slings) and Retropubic Colpourethropexy. The authors found similar efficacy between the procedures. Although they found shorter operating times and a lower incidence of post-operative voiding symptoms associated with MUS, they found that MUS were associated with a higher incidence of bladder perforations. Although the authors commented that there were less short-term complications associated with the MUS procedures, this assessment did include pain and mesh extrusion. The authors commented that "[M}ost of the trials had short term follow up and the quality of the evidence was variable."[8]

In 2011 the Cochrane Collaborative published its systematic review of 26 clinical trials of traditional slings. This review compared traditional slings to MUS and Retropubic Colpourethropexy. 12 of the reviewed trials compared traditional slings to MUS. The two procedures were found to be equally effective. MUS were found to have shorter operative times and fewer peri-operative complications with the exception of bladder perforations. The authors concluded, "Traditional slings seem to be as effective as minimally invasive slings, but had higher rates of adverse effects. This should be interpreted with some caution however, as the quality of evidence for the studies was variable, follow-up short and populations small, particularly for identifying complication rates".[9]

[8] Ogah, J, Cody, J.D., Rogerson, L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst. Rev. 2009 Oct 7;(4):

[9] Rehman H, Bezerra CCB, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD001754.

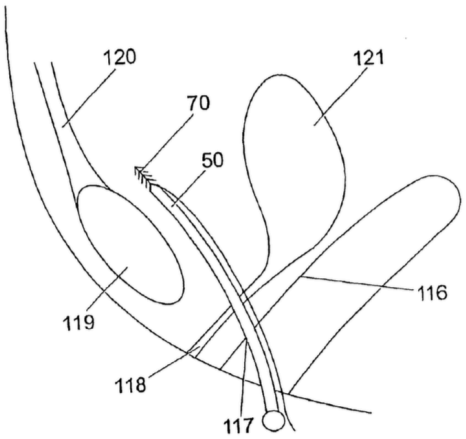
The highest level of clinical evidence, systematic reviews of RCTs shows no superiority of the MUS compared to traditional incontinence surgeries such as autologous slings or colpourethropexy. Although there is evidence that the MUS procedure is associated with shorter operative times and some evidence to suggest a lower incidence of post operative LUTs, there is no evidence to suggest that such is associated with any long term benefit. Both observational studies and RCTs do however demonstrate significant long term complications of MUS including mesh erosions and pain . With no clear efficacy benefit and no clear long term benefit of the synthetic MUS, complications such as mesh extrusion, pain syndromes, and neurologic symptoms may mitigate against the non-selective continued use of the PPM MUS and do mitigate against such use of the T.O. MUS.

The Single Incision Sling (Mini Sling)

In 2001, Dr. James Browning filed his international patent application for a novel midurethral sling. Dr. Browning reported that his invention hoped to decrease morbidity and expense of the traditional full-length midurethral sling. In 2005 the USPTO issued Dr. Browning a patent for his invention.[10] In 2003, the "MiniTape" single incision sling (SIS) of Dr. Browning was cleared by the FDA. This short sling was placed through a vaginal incision and held in place with barbed bioabsorbable soft tissue anchors. Shortly after regulatory clearance, I was hired by the company of Dr. Browning, GyneIdeas-MPathy Medical, to evaluate the product for an interested party, C.R. Bard. My evaluation demonstrated very low efficacy. C.R. Bard opted not to purchase the I.P. from MPathy.

[Figure 1: The 2001 Mini Sling Drawing of Dr. James Browning]

[10] US 6,960,160B



In 2006,Ethicon launched its version of the Mini Sling. Other companies such as C.R. Bard and American Medical Systems would launch thier SIS product shortly thereafter. All of these products were remarkably similar to the low efficacy MPathy (Dr. Browning) MiniTape.

Between the years of 2006 and 2007, I worked to solve the efficacy problem of the MiniTape. I determined that soft tissue anchors were insufficient to provide the robust short term fixation necessary for efficacy. The problem was solved with the use of an absorbable, removable, suture that would extend to the skin. Efficacy was at least as good as traditional full length midurethral slings. In 2008, MPathy Medical commercialized this improved SIS.

In the years that followed, the purveyors of the minisling would learn what I had learned five years earlier, soft tissue anchors were insufficient to allow fixation and efficacy would be unacceptably low. With the exception of my improved MiniTape, Single Incision Slings would disappear from the market.

Ethicon's Reason for Development of the TVT-S Procedure[11,12]

Ethicon's internal document provides two reasons for development of the TVT SECUR device.

Market Share and Revenue

Prior to the commercialization of the experimental TVT-S device, Ethicon was experiencing a continued loss of the sling market share. Ethicon noted that this was predominantly secondary to a loss of customers to competitive obturator slings and that recapture would be difficult. Ethicon noted in its 2004 TVTx (TVT-S project name) development contract that although its sling brand was estimated to reach 100 million dollars in sales that year, they had lost 30% of their market share to competitors. Ethicon internal documentation cited herein indicated "TVT SECUR Allows high comp advantage to regain market share" and "product innovation and advancement is required in order to stay ahead of the competition".

The following graphic from Ethicon's document demonstrates their prediction of corporate sling revenue if they do not commercialize the experimental TVT-S device and if they do commercialize the device (FIGURE 2). Similar graphics appeared in their 2004 project proposal as well as their 2006 document. The figure uses the term TVTx. This was the name of the TVT-SECUR prototype.

[11] ETH.MESH.02248848, ETH.MESH.07898852
[12] See also ETH.MESH.01279975; ETH.MESH.00596558; ETH.MESH.06927248

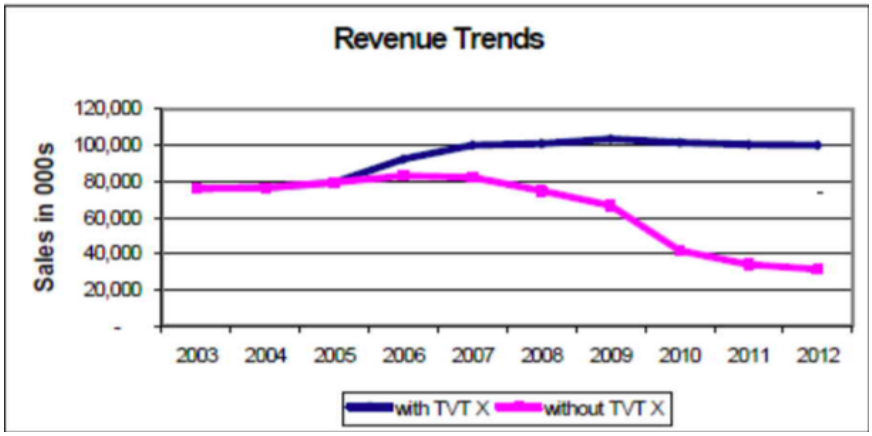


FIGURE 2: Ethicon's Projected Market Trends With and Without TVT-SECUR

Ethicon summarized their position, "TVT-S reclaims our market share" and "TVT-S protects our revenue".

Answering the question as to what validated the sales projections of the proposed TVT-SECUR device, Project Leader and TVT-S inventor stated that he believed they could use the TVT-S device to cannibalize the market as they did when they introduced the TVT-O device, "Assumptions based on the initial adoption of competitor transobturator devices, our own experience of cannibalization with TVT-O as well as independent market research".[13]

Of additional note, TVT-SECUR Project Leader noted in his 2004 proposal document "The development costs would be kept to a minimum". This is a stipulation to protect financial interests at potential risk to safety and efficacy.

Needs

Ethicon noted, in 2004, that the opportunity that merited the development and commercialization of the TVT-SECUR device was validated by customer needs. Project

[13] ETH.MESH.07898863

lead, Dan Smith, noted that the following needs were validated by independent market research:

- Better efficacy, especially in the long term
- Lower costs
- Safer Procedure / less risk of complications
- New surgical techniques to have robust clinical data
- Simpler and less invasive techniques. Drug therapies instead of surgery.
- Treatment under local anesthesia or less anesthesia, quicker recovery time, shorter hospital stay, office/out-patient procedure
- Reduced operative bleeding (offered anecdotally and not stated to be validated by market research).

Ethicon did not satisfy a single one of needs either before or after market launch.

- Better efficacy, especially in the long term: Ethicon launched the TVT-SECUR product to the open market with only 5 weeks of data from its first human trial. Even its Worldwide Medical Director questioned the efficacy found in therein, "I am not sure I agree the data looks good. You are talking about a 10% failure in the primary end point and 8/31 (25%) positive cough tests in our secondary endpoints".[14] During his deposition, Dr. Robinson admitted that the final interim data from the First Human Use Study demonstrated a high failure rate of approximately 29% and a high complication rate of approximately 65 percent. Despite these bad results, Ethicon decided to launch the TVT-SECUR, putting

[14] ETH.MESH.06151983

patients at risk of suffering significant harm and recurrent stress urinary incontinence. Interestingly, the TVT-SECUR Project Leader and inventor, Dan Smith, in his initial project proposal noted that failure to demonstrate equivalent efficacy to existing slings could result in a "no-go decision".[15] As noted in the review of the medical literature discussed elsewhere herein, the long term data established worse, not better efficacy and a higher rate of complications. Through the years following launch of the TVT-SECUR, Ethicon continued to misrepresent the results from its First Human Use Study, claiming erroneously that the study validated the safety and efficacy of TVT-SECUR.[16]

- Lower costs: Ethicon noted that it intended to launch TVT-SECUR at a price much higher price than existing products. "Current proposal is for the ASP (average selling price) to be approximate ~ 14% (13%, in EU and 15%, in US) higher than current TVT / TVTO pricing". "At the highest possible price, the product would be used in <10% of patients in Europe but nearly 30% of patients in USA". Clearly this is not intended to meet the customer need of lower cost.[17] The targeted cost of goods sold was $50.[18] The average selling price for slings in the United States at that time was $900.[19] At the proposed 15% premium, Ethicon planned to sell the TVT-SECUR at approximately $1,035. This is 2,000 percent profit margin.
- Safer Procedure / less risk of complications: Safety is demonstrated through a stepwise progression from animal labs, through small pilot human trials (e.g.

[15] ETH.MESH.07898857
[16] *See e.g.*, ETH.MESH.02113169; ETH.MESH.02113158; ETH.MESH.00008599; ETH.MESH.03235997; ETH.MESH00595165
[17] ETH.MESH.07898868**,** ETH.MESH.07898861
[18] ETH.MESH.07898866
[19] ETH.MESH.07898861

IDE), and thence through randomized controlled trials. Ethicon launched its TVT-SECUR product in 2006 having not conducted a single animal study on the TVT-SECUR device and with only 5 weeks of human data. It had skipped the necessary steps of demonstrating safety and certainly had not demonstrated a "safer procedure". What ensued was many years of experimentation on women in communities throughout the world was contemporaneous to ongoing clinical trials. Both the unconsented community experimentation and the approved post-launch clinical trials would demonstrate, as noted elsewhere herein, that the TVT-SECUR device was not a safer procedure.

- New surgical techniques to have robust clinical data: As noted herein, Ethicon planned to launch the TVT-SECUR device without robust data. Ethicon launched the product with only 5 weeks of data on 31 women.[20]
- Simpler and less invasive techniques. Drug therapies instead of surgery: As noted in the chapters of this monograph that describe the TVT-SECUR method, the "learning curve", and the teachings of Ethicon, the TVT-SECUR method was not simpler. Ethicon later noted that the TVT-SECUR had a longer learning curve than its other sling products, and even experience Key Opinion Leaders had difficulty with the instrumentation.
- Treatment under local anesthesia or less anesthesia, quicker recovery time, shorter hospital stay, office/out-patient procedure: The overwhelming majority of U.S. TVT-SECUR implantations were performed under general anesthesia.
  Reduced operative bleeding (offered anecdotally and not stated to be validated by market research): As already noted, Ethicon performed no preoperative human

[20] ETH.MESH.06893564

trials to determine if this need would be met. The subsequent unconsented experimentation as well as consented clinical trials that followed launch (as discussed elsewhere in this monograph) would demonstrate increased bleeding.

In 2008, Ethicon reported a physician survey that revealed that surgeons considered "no skin exit points" to be the least meaningful feature of its TVT-SECUR device.[21] That same poll revealed efficacy to be the most meaningful feature. Ethicon's development of the TVT-SECUR device sacrificed the most meaningful feature for the least meaningful feature

If indeed Ethicon considered there to be a safety issue with the use of the Obturator region of the body, the most reasonable innovation would be a method that did not use this area. The TVT-S utilized the Obturator Internus muscle.

In Summary, although the world always embraces safer and more efficacious procedures, the retropubic midurethral sling has an efficacy reported to be between 80 and 90% and is associated with only rare serious complications. Ethicon Worldwide Medical Director, Charlotte Owens, in her introduction to the TVT-SECUR cadaveric study, emphasized Ethicon's belief that its existing TVT was highly efficacious and associated with a low complication rate, "Records indicate that the TVT system, as of January 2005, has been used in over 650,000 cases worldwide with a very high success rate and low reported complication rate".[22]

Ethicon's development of the TVT-SECUR was not driven by its need to improve efficacy. Innovation was however needed with regard to the defective material used for such slings. Ethicon's internal documents, as noted elsewhere herein, demonstrate that

[21] ETH.MESH.09951746
[22] ETH.MESH.00403005

Ethicon had delayed the development of replacement materials, a project that would have been more attendant of the needs of surgeons and patients, for the experimental TVT-SECUR device that introduced more dangerous material (Discussed in the Material Defects section of this monograph).

If meeting a need for improved efficacy and lower complications were truly the reason for development of the TVT-SECUR device, Ethicon would have demonstrated such efficacy and safety prior to commercialization. It did not do this prior to or after commercialization. Without having any reasonable evidence to validate that the TVT-SECUR would meet any of the listed "needs" of surgeons or patients and without making any attempt to validate such, Ethicon brought the experimental TVT-SECUR device to market satisfying only one of its "Reasons for development", the recapture of market share and the maintenance of revenue.

Summary Opinion of Ethicon's Reasons for Development of the TVT-SECUR

It is my opinion to a reasonable degree of medical and professional certainty that Ethicon developed the TVT-SECUR device for the sole and improper purpose to recapture retain market share and maintain its revenue, thereby placing patients at risk of suffering unreasonable harms.

The 2005 Pre-Market TVT SECUR Studies - The Live Sheep Lab on the TVT-S Precursor, TVTx

In 2005, Rezapour et al submitted their preclinical trial which aimed at evaluation the performance of the TVTx mesh in a sheep model.[23] The description of the TVTx stated that it was made of the "same material like the standard TVT" and was coated on

[23] Rezapour, Masoumeh, Giacomo Novara, Peter A. Meier, Joerg Holste, Susanne Landgrebe, and Walter Artibani. "A 3-month Preclinical Trial to Assess the Performance of a New TVT-like Mesh (TVTx) in a Sheep Model." *International Urogynecology Journal* 18.2 (2006): 183-87.

both ends with Ethisorb. The authors offered that "Ethisorb is used as an implant in surgery for more than 10 years and there is extensive data about its safety as an implant for use in humans. The citation given for this claim was retrospective study on the use of Ethisorb to treat fractures of the orbit (the bony resting place of the eye).[24] The authors of this study concluded, "The low rate of acquired bulbus motility demonstrates acceptable results in using Ethisorb in the floor of the orbit". Although histologic evaluation was not performed, this conclusion suggests that Ethisorb creates substantial scar tissue. Interestingly, the authors reported that "The Ethisorb-coated ends of the TVTx stiffen the mesh", a characteristic not desirable in any material implanted in the vagina.

The TVTx differed from the subsequently commercialized TVT-S. The authors noted that the TVTx measured 1.1 x 12 cm. This is 4 cm longer than the subsequently commercialized version of TVTx, TVT-S. The TVTx Ethisorb, "Fleece" ends of the TVTx were barbed and the TVT-S ends were not barbed (Figure 3). The TVTx prototypes used in this animal study had either two barbs or three barbs. Additionally, the TVTx had a plastic sheathing, similar to the TVT. The TVT-S had no sheathing (Figure 4). Additionally, there were substantial method differences between the TVTx and the subsequently commercialized TVT-S. Some of these differences may have resulted in higher pullout strengths for the TVTx. By way of example, the TVTx was sutured to the tissue. This would be expected to increase resistance to pullout. Radiopaque markers were placed on the tips of the TVTx. Such markers may have increased resistance to pullout.

The investigators cut the TVTx in half prior to implantation. They impanted 4

[24] Jank S, Emshoff R, Schuchter B, Strobl H, Brandlmaier I, Norer B (2003) Orbital floor reconstruction with flexible Ethisorb patches: a retrospective long-term follow-up study. Oral Surg OralMedOralPatholOralRadiolEndod95(1):16-22

samples, paravaginally, on each side of a sheep vagina. The specimens were placed into the retropubic space (similar to the "U" method of TVT-S device). Samples were pulled out immediately (initially) and at 1, 2, 4, and 12 weeks post-implantation. The authors stated that they used a standard TVT as a control for initial pull-out force testing. The authors reported that no pullout occurred at less than five Newtons (5N). They additionally noted that a significant difference occurred in pullout force between week two and week 4. The authors stated "Two weeks after implantation, 80% of Ethisorb remained with a good tissue integration of the polypropylene mesh into surrounding scar tissue. At 4 weeks, 50% of Ethisorb were gone with a further increasing tissue integration of the polypropylene mesh into surrounding scar tissue".

The authors concluded, "The pullout forces of TVTx proved to be sufficient immediately at 1, 2, 4, and 12 weeks after implantation into the sheep's retropubic area". Based on the expected force to be encountered in the human pelvis, this statement has some merit. However, it is important to realize that this statement applies only to implantation in the retropubic space of the sheep, with a barbed Ethisorb tip, with suturing of the sling to the tissue, with an implant that was 1.1 x 12 cm (or 1.1 x 6 cm per side). Furthermore, it provides no information on how the sling might perform beyond one year and this is a permanent implant.

This statement does not indicate that a non-barbed, smaller and stiffer implant - an implant not sutured to the tissue - would have sufficient resistance to pullout. This statement does not indicate that a non-barbed, non-sutured, smaller and stiffer implant would have sufficient resistance to pullout in a human retropubic area. This statement does not indicate that a non-barbed, non-sutured, smaller and stiffer implant would have

sufficient resistance to pullout if placed in a different anatomic location, such as the obturator internus muscle.

Hence, the finding of TVTx pullout strength noted herein cannot be used to predict the pullout strength of non-barbed, non-sutured, smaller and stiffer TVT-Secur in the human retropubic space or the obturator internus muscle. Any animal study that endeavored to predict the pullout strength of a TVT-Secur device would need to use a device with similar specifications (8 cm, no barbs, non-sutured, and implanted with introducers).

The authors concluded, "Immediate pullout forces were in the range of the standard TVT". However, the authors did not provide any data on the immediate pullout forces for either the TVTx or TVT devices. Even if this data was provided, the pullout force of the standard TVT would be of little to no value. The standard TVT device does not terminate in the retropubic space. Additionally, the standard TVT is 1.1 by 48 cm and the amount of mesh subject to friction is great. Hence, meaningful data would need to include a TVT control at all measurement intervals (immediate and 1, 2, 4, and 12 weeks). This data was not collected. In summary, this study provides no evidence that the TVTx (or TVT-S) would offer similar resistance to pullout as a standard TVT placed in a human pelvis.

The authors concluded, "Histology showed good ingrowth of TVTx in the surrounding tissue with no abnormalities". However, their micrographs do not support this (Figures 4). The micrograph of the Ethisorb "sandwich" at four weeks show no tissue integration between the pieces of Ethisorb. This is consistent with Ethicon's description

of Ethisorb as being an "impermeable sheet of material".[25] Furthermore, the 12-week micrograph shows almost no ingrowth between the mesh fibers and a loss of connective tissue surrounding the fibers. This is consistent with the destruction of collagen and elastin associated with polypropylene mesh.[26]

The authors concluded, *"The data collected in this study show the proof of principle of TVTx and could support the realization of clinical trials with the TVTx mesh"*. This statement is correct. The study showed that TVTx had a good resistance to pullout, and this study could be used as evidence to support a clinical trial for TVTx. However, this study did not show proof of the principle of TVT-S and could not have been used as evidence in support of a clinical trial for TVT-S. This study, however, should have been used as evidence to support a trial in live animals on TVT-S.

In summary, Rezapour et al have demonstrated that a novel 12 cm sling, with impervious Ethisorb barbed ends, has good resistance to pullout when inserted in the retropubic space of a sheep. Their micrographs demonstrate that the impervious Ethisorb prevents tissue integration into the mesh at four weeks and there is little tissue integration at 12 weeks (Figure 5). Although their study provides no data to support a human trial of the TVT-S device, it does provide evidence that could have been used a part of a larger group of evidence, to support a human trial of the TVTx device. That larger group of evidence would need to include safety testing of the both the Ethisorb material and PROLENE sandwiched Ethisorb material in the human vagina.

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[25] **K991413**

[26] Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. BJOG 2013;120:233-43.

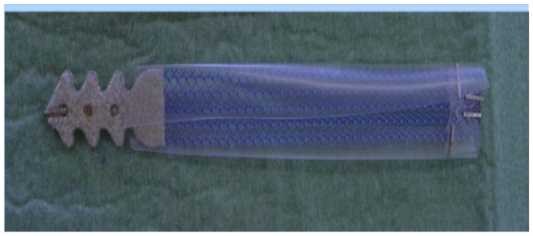

Figure 3: TVTx with sheathing and 3-barbed Ethisorb end

Figure 4: TVT-S has no sheathing around sling and no barbs on Ethisorb end.

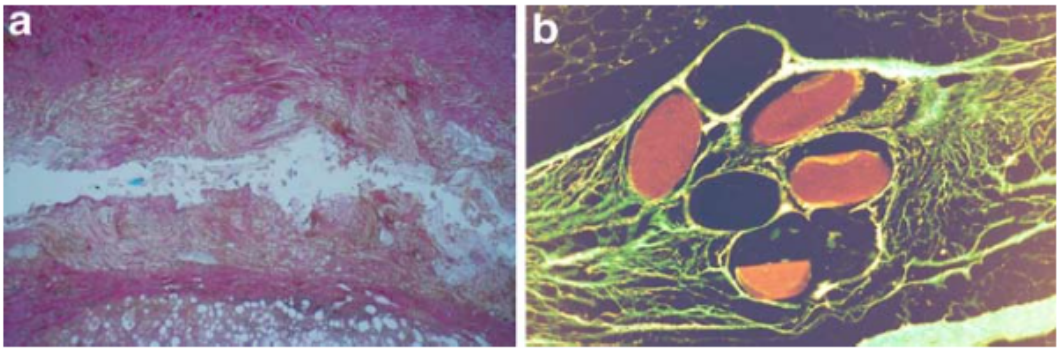

Figure 5: Microphotographs

The Cadaveric Sheep Lab on the Modified TVTx, the TVT-SECUR

EVALUATION OF FIXATION FORCE FOR THE GYNECARE TVT SECUR DEVICE IN A SHEEP CADAVER PELVIC FLOOR MODEL [27]

Following the TVTx live sheep lab, modifications were made to the TVT-SECUR inserter and the TVT-SECUR sling (the Christmas tree, barbed, ends were made removed). Ethicon conducted this cadaveric lab to evaluate these changes to the TVTx device. The new, modified device, was called the TVT SECUR.

[27] ETH.MESH.00749504

Purpose

"The primary objective of this study was to assess and document the security (i.e. fixation force) of the GYNECARE TVT S end design at the time of implantation in the sheep pelvic floor model by comparing it to a 164 gram pullout force".*

Ethicon's internal testing had demonstrated that 164 grams represented the force at which its mesh became permanently deformed. Ethicon also noted that a recent study had demonstrated that a sling, in vivo, was exposed to approximately 50 grams of force.[28]

"The secondary objectives were: (1) to examine the Inserter removal force of the GYNECARE TVT S device after the release wire has been released , and (2) to compare the GYNECARE TVT S fixation force results with TVTx fixation force results in Ethicon Study"*

Acceptance Criterion

Ethicon had determined that the TVT-S would demonstrate acceptable performance if no more than two of ten TVT-S implants pulled out (allowing for an 80% confidence interval, an 8 out of 10 success rate could represent a 6 out of 10 real success rate (60%). Ethicon determined that 60% success (based on an 80% CI) would be acceptable. Ethicon also built in a back-up plan. Should the TVT-S not meet this 60% success rate acceptance criteria, it would still deem the device acceptable if it was at least 70% as successful as the TVT device.

[28] ETH.MESH.04385242 and Lin, A TT, Wang, SJW, Chang, LS: In Vivo Tension Sustained by Fascial Sling in Pubovaginal Sling Surgery for Female Stress Incontinence. J Urol, 173:894, 2005

Experimental Design

Ethicon implanted each of five sheep cadavers with 1 TVT device and 2 TVT-SECUR devices. The TVT device was implanted first. If the TVT device pulled out with less than 164 grams of force, the cadaver was deemed unacceptable for implantation. Ethicon tested the pull out force of each sling as well as the pull out force of the inserters.

Results

All TVT-SECUR and TVT implants withstood the 164 gram pull out criteria. Based on this, the TVT-SECUR met both acceptance criteria and was considered a success.

No significance was noted between the pull out force for the TVT-S device noted in this cadaveric sheep study and the immediate pull out forces previously noted when the TVTx device live sheep study. The TVT-SECUR inserter pulled out with a mean of 944 grams of force (standard deviation of 508 grams).

Summary Of TVT--SECUR Cadaveric Sheep Study

The pull out force of the TVT-SECUR sling may be adequate, immediately after insertion, in a dead sheep: This study in no way demonstrated that the TVT-S sling had the sufficient resistance to post-implantation movement required to provide clinical efficacy. This study only demonstrated that the TVT-SECUR device had an immediate resistance to pull out in a dead sheep that was not significantly different than the immediate resistance to pull out in a live sheep. Whereas the TVTx (barbed TVT-SECUR precursor) was testing for pull out force on living sheep immediately after implantation and at 1, 2, 4, and 12 weeks, Ethicon chose only to test the TVT-S on for immediate pull out on a dead sheep.

No conclusions or even meaningful assumptions can be made to how the TVT-SECUR device would perform on a live sheep. In order for a sling to be efficacious, it must resist movement during the first one to two weeks following implantation. Ethicon made no attempt to assess the TVT-SECUR in a live animal. It is unclear why Ethicon chose not to test its TVT-SECUR device in the same manor it tested its precursor TVTx device.

However, even if it had and the results were the same, it would have only demonstrated that the device resisted expected pull out forces in the retropubic area of a sheep. This information would need to be submitted to an IRB or the FDA (for IDE) as supporting evidence for a subsequent small human safety trial to be followed by an RCT for both safety and efficacy. Ethicon was well aware of such standards. In a later email chain between Dan Smith, TVT-SECUR project leader, Ethicon's Jason Hernandez, and Ethicon's paid TVT consultant, Dr. Carl Nilsson, Mr. Hernandez noted that "all iterative changes would require an FDA IDE".[29]

The TVT-SECUR inserter required too much force to remove and this most likely contributed to clinical failures: The mean pull out force required to remove the inserter was 944 grams and may have been as high as 1,452 grams (reported standard deviation). The mean pull out force of the TVT-SECUR sling was 1095 grams and may have been as low as 538 grams (reported standard deviation). The force at which the TVT-S sling is expected to permanently deform (become like a "rope") is 164 grams. These numbers represent a perfect set up for failure and complications.

In the event that an inserter was to pull on the sling during removal, the force on the sling would between 5.7 and 8.8 times the force known to permanently deform or

[29] ETH.MESH.04048515

"rope" the PROLENE mesh of the TVT-SECUR device. Roping is a known cause of pain and erosion. In the event that the inserter was to pull on the sling during removal, the force on the sling would be expected to result in frequent dislodgment of the sling (as often as half the time). Dislodgment is a known cause of clinical failure.

The Four Human Cadaver TVT-SECUR Pull Out Force Lab

EVALUATION OF THE PULLOUT FORCE OF GYNECARE TVT SECUR IMPLANTED INTO THE UROGENITAL DIAPHRAGM AND OBTURATOR MEMBRANE OF A HUMAN CADAVER[30]

On August 15th of 2005 Ethicon evaluated the pull out force of its experimental TVT SECUR device on four refrigerated human cadavers.

Primary Objectives:

> "(1) to assess and document the security (i.e. pullout force) of the GYNECARE Tension-free Vaginal Tape SECUR* (GYNECARE TVT S*) end design at the time of implantation in the urogenital diaphragm and obturator membrane; (2) to detennine the security of GYNECARE TVT S following insertion, removal and reinsertion in a site close to the site of the first insertion. The secondary objective of this study was to examine the Inserter removal force of the GYNECARE TVT S* Implant after the release wire has been pulled".

Acceptance Criteria:

Ethicon had determined that the TVT-S would demonstrate acceptable performance if 58% of pulls resisted 164 grams of force. The rationale for such has was the same as that presented sheep cadaver lab described previously in this monograph. Should the TVT-S fail to meet this acceptance criteria, Ethicon provided that a success rate equal to 69% of the TVT and TVT-O would be acceptable.

Experimental Design:

The TVT and TVT-O were first implanted in the retropubic and obturator tissues. If the pull out force was greater than 164 grams, the cadaver tissue was deemed

[30] ETH.MESH.00072085

acceptable and the TVT-SECUR devices were implanted. Implantations were made and pull out strengths measure. Implantations were repeated by pulling out the inserter and replacing it. Such replacements were made in adjacent and contiguous insertion sites.

Results:

Numerous issues that biased the results were encounter.

One of the five cadavers (cadaver 2) was excluded because it was felt to be cachectic with tissue deterioration. This is a subjective determination and obviated the objective 164 gram minimum pull out exclusion criteria. If Ethicon felt that its device might only perform well on the most robust specimens, it could exclude any specimen it wanted by calling it cachectic.

The plan to make adjacent implantations failed. Ethicon indicated that there was not enough space. It determined this after performing adjacent implants on cadaver number one. It opted not to include these pull out forces in the data set. As a result, data was only recorded and analyzed for the first insertion each device and the subsequent close insertion (the contiguous or "adjacent" insertions were not made as planned). Numerous data points were missing from the data set. Ethicon chose not to analyze all insertions but rather to analyze "(Cadaver 1, 3, 4 & 5 Insertion #1) and the implantation of each device close to the first insertion (Cadaver 1 - Insertion #3 and Cadavers 3, 4 & 5 - Insertion #2)"One of eight TVT-S first insertion pull out forces and two of the second insertion (close) pull out forces were not included in the analysis.

In cadaver number 3, the TVT-SECUR sling became dislodged whilst removing the inserter. Hence, a pull out force that, more likely than not was low, was not recorded.

Although it remains unclear which insertions were included and excluded from the data set, the computations generated from the data set demonstrated no statistical difference between the pull out strengths of the TVT-SECUR device and the TVT and TVT-O devices. Ethicon reported that 7 out of 7 urogenital (retropubic) TVT SECUR implants and 8 out of 8 Hammock TVT SECUR implants achieved acceptable pull out resistance (greater than 164 grams) and also met the ratio criteria for acceptance (compared to TVT O and TVT). Ethicon noted that there was a significant decrease in resistance to pull out between the first and second TVT SECUR insertion (urogenital diaphragm).

Summary of the TVT-SECUR Human Cadaveric Pull Out Testing

Although Ethicon concluded that there was no significant difference between the TVT-SECUR pullout strength and the TVT and TVT-O in four human cadavers, there is missing data. If the missing data was treated as failures, the analysis may have not met acceptance criteria. There is no way to know if pull out strength in a refrigerated human cadaver in any way correlates with the pull out strength in a live human. As neither the TVT-O nor the TVT were ever used for a single incision sling, there is no way to know if the pull out strength of the TVT-SECUR must be similar or greater than those devices. Indeed, without the benefit of penetration through the rectus fascia and obturator membrane (and muscles), the resistance to pull out of the TVT-SECUR device may very well need to be several times that of an anchorless TVT-O or TVT as tested in a single incision experiment.

In summary, Ethicon may have shown that the TVT-SECUR resistance to pull out in four refrigerated human cadavers is similar to that of TVT and TVT-O. However,

Ethicon had no idea if such would be sufficient to preclude clinical failure. Ethicon noted that it chose 164 grams as a cut off acceptance criteria as this is the force that causes permanent deformity and roping of its mesh. This roping is routinely noted in clinical practice suggesting that it is not uncommon for the TVT to be exposed to greater forces or, more likely, that the mesh undergoes permanent deformity and roping at forces less than 164 grams.

Of additional note, Ethicon found that there was a significant decrease in resistance to pull out (urogenital diaphragm) on a second insertion. As Ethicon chose not to label its device to caution against multiple insertions, Ethicon needed to further evaluate the risks of multiple insertions. It is likely that that a larger more robust study would demonstrate a high failure rate.

Similar to the cadaveric sheep study, the pull out force of the inserter raised substantial concern for sling dislodgement. The community, following commercialization of the TVT SECUR device, later validated this concern. The mean pull out force of the inserter was 532 grams and as high as 731 grams (standard deviation). The resistance to pull out of the TVT-SECUR Hammock and TVT Secur U were less than 305 grams in 12% and 14% of implants respectively. Hence, in approximately 13% of cases, the force required to remove the inserter was likely to be greater than the force required to dislodge the sling. This would be expected to result in clinical failures.

Summary Opinion of Human Cadaveric TVT-SECUR Pull Out Force Lab

It is my opinion to a reasonable degree of medical certainty that:

- the 4 human cadaver TVT-SECUR lab in no way provided any evidence of adequate resistance to pull out in living human.

- there was no data and Ethicon conducted no study to demonstrate that there was any correlation between pull out strength in the urogenital diaphragm of a cadaver and the urogenital diaphragm of a living women.
- there was no data and Ethicon conducted no study to demonstrate that there was any correlation between pull out strength in the obturator space of a cadaver and the obturator space of a living women.
- the cadaveric test performed herein by Ethicon is representative of testing typically used to support applications to the FDA or an IRB for a human safety trial and not representative of a study used to provide the safety or efficacy data needed for commercialization of a medical device.
- Ethicon understood that cadaveric tissue was non representative of living tissue yet Ethicon inappropriately opted to bypass live animal testing on its TVT-SECUR device.[31]
- the TVT-SECUR human cadaver lab further validated the concerns for sling dislodgement by inserter removal, concerns raised by the TVT-SECUR cadaveric sheep study, yet Ethicon opted not to address this problem or warn of such in its IFU.
- the TVT-SECUR human cadaver lab demonstrated an increased risk of TVT-S failure with a second insertion yet Ethicon opted not to warn of this in its IFU label.

[31] Ethicon performed live animal testing on its TVTx device and opted not to perform it on its TVT-S device.

- Ethicon's own study demonstrated that adjacent (contiguous) reinsertion represented a unique risk (compared to "near" reinsertion) yet failed to evaluate this risk or warn of such risk in the TVT-SECUR IFU or otherwise.
- Ethicon or its employees understood that adjacent (contiguous) reinsertion represented a unique risk (compared to "near" reinsertion) yet failed to evaluate this risk or warn of such risk in the TVT-SECUR IFU or otherwise.

The Single Surgeon TVT-SECUR Human Cadaver Lab

GYNECARE TVT SECUR CADAVER PROTOCOL & COMPLETION REPORT[32]

On August 8th of 2005, approximately three weeks after completion of the cadaveric sheep lab, Ethicon conducted a human cadaver lab to study its experimental TVT-SECUR device.

STUDY RATIONALE

"The project team has planned and is conducting a series of tests to evaluate the passage, final position, and proximity to structures of interest to a surgeon for the TVT-SECUR* System; "U" and "hammock" approaches".

STUDY METHODS

The methods section of the protocol stipulates that surgeons with experience in performing TVT retropubic and TVT obturator sling surgeries would be chosen. The method section further stipulates that the surgeon would be required read and be knowledgeable of the contents of the IFU. An Ethicon R&D associate would review the procedural steps guideline document and IFU with the surgeons. The surgeons would be required to watch a TVT-SECUR procedural video. The surgeons would have the

[32] ETH.MESH.00403003

opportunity to ask questions prior to the procedure. Following the placement of the TVT-SECUR device by means of both the "U" and the "Hammock" method, the surgeons would be required to complete questionnaires and have the opportunity to provide additional comments.

RESULTS

Although the methods section indicated that experienced surgeons would be chosen, the TVT SECUR CADAVER PROTOCOL & COMPLETION REPORT provides results from only a single surgeon on a single cadaver.

Hammock Method Results

The records indicate that surgeon, Dr. Bob Rogers, accidentally entered the space of retzius. This entry was noted to have traumatized the blood vessels of Santorini. This would have been expected to cause significant bleeding in a live surgery. The records indicated that this was secondary to improper placement. The records further indicated that "a few attempts" were required to obtain correct placement.

The records indicate that Dr. Rogers believed that the TVT-SECUR Hammock method is capable of causing bowel injury. Dr. Rogers stated "If put in correctly, it should not enter bowel". Ethicon's TVT-SECUR expert witness opined that bowel injuries to occur with the TVT-SECUR device.[33]

Hammock Method Human Cadaver Results Summary

The single experienced surgeon operated on a single human cadaver. The surgeon noted that it took several attempts for him to achieve proper placement. In the course of attempting to achieve correct placement, the surgeon entered an unanticipated anatomic area and penetrated blood vessels. Such penetration would be expected to cause

[33] TVT-SECUR expert opinion of Dr. Brian Flynn pg 44

hemorrhage in a live patient. The surgeon also believed the hammock method had the potential of bowel injury.

"U" Method Results

Dr. Rogers injured the veins of Santorini on his first two attempts to pass the right side of the TVT-SECUR device. Dr. Rogers noted that he believed that the TVT-SECUR device did not offer a lower risk of this complication than the TVT device.

Failure to Evaluate Obturator Vessel Injury and Patient Positioning

Obturator Vessel Injury

The experimental TVT-SECUR device and method involved the placement of a large, novel, stiff, sharp sling end into the obturator internus muscle. Although Ethicon asked Dr. Rogers to examine the proximity of the TVT-SECUR sling to the Obturator bundle (the structures passing through a single area known as the obturator canal), no evaluation was made with regard to the proximity of the device to the obturator internus muscle's own blood supply. Following commercialization, the TVT-SECUR device and method were found to be associated with an increased incidence of obturator space hemorrhage (discussed elsewhere herein). A cadaver lab performed several years after commercialization found that the TVT-SECUR inserter to pass only 5 millimeters from the blood supply to the obturator internus muscle.[34] The TVT-SECUR sling is 11 millimeters wide. Ethicon failed to evaluate the anatomic relationship its experimental TVT-SECUR device and the blood supply muscle it penetrated.

[34] Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88 (Concluding that "TVT-S has a high risk of placement into the small pelvis with risk of injury to vessels, urinary bladder and variable anatomical structures. Excessive movement with the inserter might cause severe complications. In the case of perforation of the fascia of obturator internus muscle, hemorrhage will be less likely to stop by self-compression").

Patient Positioning

Both the inventor of the obturator sling method, Dr. Delorme, and Ethicon's Worldwide Director of medical affairs have recommended hip flexion when placing materials into the obturator space.[35] Ethicon failed to evaluate the effects of hip flexion on its experimental TVT-SECUR device and in toward out method. Dr. Delorme taught 120 degrees of flexion. Hinoul et al determined that flexion of less than 80 degrees was dangerous bringing the instrumentation to within 5 millimeters of the obturator bundle. Flexion of greater than 100 degrees was protective. Ethicon opted not to evaluate the effects of patient position on the TVT-SECUR's risk of nerve and vessel injury. The IFU provided no guidance on this critical procedural step.

Summary of Pre-Market Clinical Testing

Ethicon's pre-market clinical testing of its experimental, novel, TVT-SECUR device was limited to a single cadaveric sheep pull-out force, a single four-cadaver human pull-out force study and a single, one cadaver-one surgeon lab to evaluate the passage, final position, and proximity to vital structures. Both the sheep and human cadaver studies raised substantial concerns with regard to the risk of sling dislodgement. No further studies were performed.

The evaluation performed on a single human cadaver by a single surgeon raised substantial concerns for the inability to correctly insert the experimental sling as well as concerns for bleeding complications. Ethicon opted not to perform any testing of its experimental TVT-SECUR device on a living organism. No live animal studies were

[35] Hinoul, Piet, Linda Vanormelingen, Jan-Paul Roovers, Eric De Jonge, and StÃ©fan Smajda. "Anatomical Variability in the Trajectory of the Inside-out Transobturator Vaginal Tape Technique (TVT-O)." *International Urogynecology Journal* 18.10 (2007): 1201-206., Delorme patent US 6,638,211 B2, Emmanuel Delormea, Ste´phane Droupy b, Renaud de Tayrac c, Vincent Delmas. TransobturatorTape (UraTape®): A New Minimally-Invasive Procedure toTreat Female Urinary Incontinence. European Urology 45 (2004) 203–207

performed. No human safety or efficacy studies were performed. With no meaningful animal safety or efficacy data, Ethicon would initiate its first human trial. At the time of TVT SECUR commercialization, only five-weeks of human data in only 31 patients was available. As noted elsewhere herein, the data was not reassuring.

Summary Opinion of Pre-Market Clinical Testing

It is my opinion to a reasonable degree of medical and professional certainty, as both a medical and industry expert, that:

- Ethicon failed to perform adequate pre-market pre-clinical and clinical testing necessary to demonstrate efficacy, failed to perform the pre-market clinical testing necessary to demonstrate safety, and failed to perform the pre-market clinical testing necessary to protect women from harm.
- As evidenced by the initial testing of the TVTx on live sheep and internal documents reviewed elsewhere in this monograph, that Ethicon was aware that it had not demonstrated safety and efficacy prior to commercialization of its experimental TVT-SECUR device and intended to commercialize the experimental TVT-SECUR device without such demonstration.

Clinical Expert Report GYNECARE TVT SECUR System[36]

This report was authored and signed by Martin Weisberg, M.D., Ethicon's Senior Medical Director, on December 2nd of 2005. Dr. Weisberg began his report "This report summarizes preclinical data and proposed use and offers a clinical opinion of GYNECARE TVT SECUR, a new approach to midurethral tension-free support". Dr. Weisberg than offers a background of the treatment of incontinence. He reports that

[36] ETH.MESH.04385229

published literature for retropubic sling shows a bladder perforation rate of 3.8%. He then notes that the Ethicon complaint database demonstrated only a 0.002 incidence of bladder perforation.

This demonstrates the well-known underreporting of complications noted in corporate databases. This information should have alerted Ethicon of the need to multiply the complication rate in its databases by as much as 1,900 times to determine the probable complication rates in the community. Dr. Weisberg added that perforation of large blood vessels and intestinal viscera had been reported in the literature and the obturator approach is associated with thigh pain. Dr. Weisberg stated the TVT-SECUR device eliminated or reduced these complications.

As is noted elsewhere in this monograph, at the time of the writing of this report, Dr. Weisberg had no human data to support this claims. Furthermore, the limited cadaveric data suggested that his claims would unlikely be true. Other than a slight decrease in discomfort during the first few weeks following surgery (not resulting in any decreased in pain medication usage), years of experimental use on the public and clinical trials would fail to validate his claims.[37]

Device Description

Dr. Weisberg described the TVT-SECUR device. In this description he disseminated incorrect and misleading information.

> The mesh of the TVT-SECUR was made of PROLENE" and "This material (PROLENE), when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use"and "studies show that implantation of PROLENE mesh and the absorbable fleece sandwich material made from VICRYL and PDS yarn elicit a minimal inflammatory reaction in tissues, which is transient and is followed by the deposition of a thin fibrous layer of tissue.

[37] Evidenced throughout this monograph.

As discussed in detail in the material defects chapter of this monograph, the PROLENE mesh is now well-known not to be inert and the inflammation is not transient. Ethicon's own animal studies showed persistent inflammation without resolution. The medical and scientific literature have demonstrated the polypropylene mesh is not only reactive and inflammatory in perpetuity, but it destroys tissue.[38]

> *"The resultant fleece material is of sufficient pore size to allow continuing growth of cells and intrinsic body tissue" and "The fleece layers are replaced as connective tissue grows into the mesh".*

This claim is in direct contradiction of Ethicon's description of its fleece material provided by Ethicon to the FDA. Ethicon describes its fleece material as being an "impermeable sheet of material" and allowing tissue "on-growth" (not ingrowth).[39] Furthermore, as discussed elsewhere herein and shown by micrograph, there is virtually no ingrowth of tissue into the fleeced ends of the TVT-SECUR sling.[40]

> *"The PROLENE material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes".*

As discussed in detail in the material defects chapter of this monograph, polypropylene is highly reactive causing a chronic inflammatory response and chronic foreign body reaction and degrades following implantation in the human body. This is a fact that is validated in the medical and scientific literature and also validated by both Ethicon's own internal studies, by its own scientist and by its own medical director.[41]

> *"PROLENE mesh is knitted by a process that interlinks each fiber junction and which provides for elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body".*

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[38] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J.17.S1 (2006): 26-30., Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. BJOG 2013;120:233-43.

[39] K991413

[40] Rezapour, Masoumeh, Giacomo Novara, Peter A. Meier, Joerg Holste, Susanne Landgrebe, and Walter Artibani. "A 3-month Preclinical Trial to Assess the Performance of a New TVT-like Mesh (TVTx) in a Sheep Model." *International Urogynecology Journal* 18.2 (2006): 183-87.

[41] ETH.MESH.01264260 (Presentation, "Prolift+M," P Hinoul, MD, Ethicon Pelvic Floor Expert's Meeting – Nederland, Utrecht, May 7, 2009). See deposition of Daniel Burkley (5/22/13) 108,206,315

As discussed in detail in the material defects and labeling defects chapters of this monograph, there is neither clinical nor scientific evidence to validate bidirection elasticity following implantation. Indeed, the medical and scientific literature has shown that almost all elasticity is lost and the mesh becomes inelastic and brittle. Dr. Weisberg misleads the reader to believe that elasticity noted prior to implantation is maintained post implantation, adapting "to the various stresses encountered in the body".

> *The polypropylene mesh utilized in TVT SECUR differs from the mesh used in previous TVT products in that the mesh in TVT SECUR is laser cut rather than mechanically cut. The physical properties of the laser cut mesh are clinically equivalent to the mechanically cut mesh and the particle loss is less".*

As described in detail elsewhere in this monograph, Ethicon purposefully altered the physical characteristics of the TVT-SECUR mesh through the process of laser cutting. Ethicon's TVT-SECUR Project Leader, engineer and inventor, Dan Smith, has stated, "The short laser cut mesh does not stretch the same as a full length mechanically cut TVT-O, or even as much as a full length LC TVT-O meshes".[42] Mr. Smith, when describing the laser cutting of a PROLENE sling, stated, "TVT-O MC (mechanically cut) is used, by more than 90% of all TVT-O user! This means that as TVT-O users are converted they will have early failures as did TVT SECUR until they figure out that a mini-sling needs to be placed differently (tighter) due to the mesh properties" (short, stiff, laser cut mesh).[43] Clearly, Dr. Weisberg's claim that the "*physical properties of the laser cut mesh are clinically equivalent to the mechanically cut mesh"* are incorrect, misleading, and is in direct conflict with the known and intentionally altered properties of the TVT-SECUR mesh.

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[42] ETH.MESH.09911297
[43] ETH.MESH.09911297

Dr. Weisberg provided a "cut and paste" of the TVT-SECUR IFU as part of his narrative. The numerous defects of this label are discussed elsewhere in this monograph.

Pre-Clinical Evidence

Dr. Weisberg reported that the TVT SECUR components and procedure had been developed with surgeons and had been "studied, refined, and validated in human and animal cadaver studies".[44] However, the inventors shown on the related patents are void of surgeons and, as noted elsewhere herein, the TVT-SECUR components and procedure were certainly not validated by the single sheep cadaver lab and one human cadaver evaluation. Dr. Weisberg added that the TVTx live sheep study demonstrated "good in-growth of the surrounding tissue into the mesh with no abnormalities".

As described elsewhere herein, the TVTx is not representative of the TVT-SECUR device and the referenced study showed minimal to no tissue in-growth with evidence of tissue destruction. Dr. Weisberg states that a human cadaver lab demonstrated adequate fixation of the TVT-SECUR. As noted elsewhere herein, such was not the case. Dr. Weisberg stated that the pull out force for the TVT-SECUR device had been shown to be similar to the conventional TVT. This misleads the reader to believe that the experimental TVT-SECUR device had been adequately tested and could be expected to provide the same resistance to pull out, in clinical use, as the TVT device. However, the truth was that Ethicon had only evaluated the comparative pull out force in a the retropubic of sheep and four refrigerated human cadavers. Ethicon had no evidence to demonstrate there was clinical equivalence.

Dr. Weisberg added that the pull-out forces were similar between the TVT-SECUR hammock method and the traditional transobturator slings. This is a misleading

[44] ETH.MESH.04385241

statement. A less misleading and correct statement would be that a small human cadaver study failed to show a significant difference in pullout strength.

Dr. Weisberg's Summary

> *"Additional clinical studies to support the safety and effectiveness are not necessary prior to release of the product"*

In the TVT-SECUR clinical expert report, dated December 5, 2005, Dr. Weisberg concluded:

> Based on the facts that the implanted mesh in TVT SECUR is the same as the currently marketed TVT mesh products, in terms of indications for use, material, construction and key dimensions, (i.e. the width and thickness of the "working" section), the preclinical studies of the GYNECARE TVT SECUR System for Incontinence and the clinical history of predicate tension-free midurethral polypropylene slings, specifically GYNECARE TVT and GYNECARE TVT Obturator, and the risk assessment performed for the device, it is my opinion that the GYNECARE TVT SECUR System for Incontinence is a safe device that will be effective for the treatment of urinary stress incontinence resulting from urethral hypermobility or intrinsic sphincter deficiency. Additional clinical studies to support the safety and effectiveness are not necessary prior to release of the product.

As noted in this chapter and throughout this monograph, the Ethicon deliberately altered the material properties of the TVT-SECUR to be different than its other full-length TVT mesh products and the preclinical studies in no way demonstrated safety or efficacy, and there was no basis for a determination of safety or efficacy.

Moreover, Dr. Weisberg signed off on the safety and efficacy of the TVT-SECUR product before the First Human Use Study even started and nearly a year before the interim data was available to Ethicon. Despite this, Dr. Weisberg signed off on the safety and efficacy of the TVT-SECUR device and permitted it to be launched worldwide for use as a permanent medical device to be implanted in women around the world without any human safety or efficacy data. Moreoever, when the final interim data results

became available on September 12, 2006, demonstrating an unacceptably high rate of failures and complications, the Clinical Expert Report was not revisited and the TVT-SECUR was launched worldwide just eight days later, as discussed in greater detail herein.

Summary Opinion of Dr. Weisberg's Clinical Expert Report

It is my opinion to a reasonable degree of medical and professional certainty that:

- Dr. Weisberg caused physicians to be misled to believe that the experimental TVT-SECUR device is inert, associated with tissue integration rather than destruction, and that Ethicon had demonstrated efficacy and safety.

- Dr. Weisberg's granting of permission to proceed to market without further safety or effectiveness studies was dangerous, inappropriate, and not supported by the scant testing performed by Ethicon.

  Dr. Weisberg's granting of permission to go to market without further safety and efficacy testing was done for the sole and improper purpose of getting or attempting to get the TVT-SECUR to the market before its competitors in an effort to recapture or retain its market share which Ethicon projected would be lost without a quick commercialization of a mini-sling, as demonstrated through Ethicon's internal company documents and referenced at length elsewhere herein.

The 2005 Pre-Market Design Validation Report[45]

The Design Validation Study is part of the worldwide industry standard for risk management and is also described in ISO 14971 (Risk Management for Medical Devices).

The purpose of the design validation study was stated as:

> The purpose of this study was to provide objective evidence that the GYNECARE TVT SECUR SYSTEM (including devices, packaging, and labeling) satisfies defined user needs and intended uses within actual or

[45] ETH.MESH.00325942

> simulated-use environments in a manner consistent with the Instructions for Use (IFU) for GYNECARE TVT SECUR SYSTEM and the OR staff's and surgeons usual techniques. A further purpose of this study was to ensure that the clinical user encounters no unanticipated functional, safety, or human factors issues during normal use of the device, including removal from the package and adequacy of the package insert.

The Design Validation Study failed to achieve its intended purpose, validation of the TVT-S SECUR design and IFU. Although thirteen surgeons participated in validation cadaver lab, the handwritten questionnaires from two of these surgeons were lost. The chosen surgeons were Ethicon Key Opinion leaders and "All surgeons routinely work in the women stress urinary incontinence treatment".

Prior to evaluation of the product, study participants were "trained by appropriate ETHICON representative", "saw and reviewed the Big Print of the Procedural Steps Guide Line", saw and reviewed a video of the procedure, and read the IFU. The videos showed the complete procedures. The Design Validation Report noted that these items were used "to provide appropriate instruction".

The Design Validation Report noted that 50% the surgeons in the "original part" of the design validation had issues with the procedure. One experienced surgeon placed the TVT-SECUR into the bladder. Another experienced surgeon forgot to remove the protective cover. Although Ethicon blamed these issues on user error, the IFU plus additional training is meant to prevent such error. The IFU is meant to provide a surgeon with the necessary instruction to perform a procedure safely and effectively.

Based on the failure to validate the design, Ethicon stated that it revised the IFU with new pictures and text and the Key Procedural Steps Guide Line Big Print document. This was called "Amendment 1". Following this, the Design Validation team conducted

what it labeled "Part 2" of the validation. Three surgeons performed only the U approach. The document does not indicate if these surgeons were new, surgeons from the "original part", or included the surgeons who had issues during the "original part".

The Design Validation report states that there were no bladder or protective cover issues. Unfortunately, this does not validate that the changed documents were effective. In the "Original part" one in four surgeons penetrated the bladder with TVT-SECUR and one in four forgot to remove the protective sheath. With a 25% rate of such complications, it would be unlikely for such to occur in a "Part Two" with only three surgeons. Indeed, there would be a 75% chance that such issues would not be noticed (even with no update to the labels).

Additionally, one third of the surgeons in "Part 2" experienced two new issues; the TVT-SECUR sling was dislodged while trying to remove the inserter and the insert release wire inadvertently pulled free. The design validation team stated that the release wire issue was related to a manufacturing problem that had already been corrected. They attributed the dislodgement of the sling to be user error, claiming that Dr. Iglesia did not follow the clearly stated training instructions to gently, with a slight twisting motion, remove the inserter. This expert surgeon not only read the IFU, she watched a training video, was trained by Ethicon, and read the Big Print Guide line document".

If indeed she failed to follow the IFU, this indicates a need for an improved emphasis on this portion of the IFU. Ethicon apparently agreed with my comment as it updated the IFU instructions by changing the font to bold for the sentence teaching removal of the inserter. Ethicon also updated the "Key Procedural Steps Guidelines" document. Ethicon called these changes "Amendment 2".

Ethicon than went on to perform what is labeled as "Part 3" of its design validation study (with updated, Amendment 2, documents). Three surgeons performed only the "U" approach. There was no dislodgement of the tape with removal of the inserter. There was another release wire problem. This was attributed to the already identified manufacturing process that was stated to have been corrected.

As the dislodgment of the sling during removal of the inserter happened in 33% of the procedures in Part 2, without any change to the IFU and Guidelines document, the odds would favor not experiencing such dislodgement in this Part 2 analysis. In order to demonstrate that the change in the documents corrected the defective label, a much larger sample was needed. Ethicon noted that a Part 4 would be performed to determine if the new manufacturing process had resolved the spring wire issue.

Although Ethicon reported no wire problems in Part 4, this part involved only three surgeons and six passes of the inserter. Wire problems were noted in 17% of inserter uses. Even without any update to the labels, the odds favored a failure to observe the identified wire issue in Part 4. A much larger sample would be needed.

Of note, the 17% incidence of inserter related problems identified in this design validations study is identical to the percentage of TVT-SECUR Medical Device Reports to the FDA represented by inserter problems (17% of TVT-SECUR MDRs are related to the inserter mechanism). Inserter related problems were the most common procedure related MDR.[46,47]

One October 25th of 2005, in response to Dan Smith's refusal to revise the TVT-IFU, based on suggestions from an investigator who participated in a design validation

[46] See FDA MAUDE database

[47] A post-market study published by Hubka et al. correctly noted that "[e]xcessive movement with the inserter might cause severe complications." Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88

study, Gary Borkes wrote: "Please don't take this the wrong way……. But why do you think we are doing Design Validation exercises? It is not just another hurdle to "pass", although I get the impression that some might feel that way. The reason we take the device to users in Design Validation is to illicit their input, not to help or coach them to pass a test. It is to confirm the product meets their needs, including packaging and labeling" and further that "the timeline pressures are recognized and felt by everyone – believe me Dan everyone I talk to says how under the gun they are and how much they are trying to push to support you and the project despite the overwhelming load (even me – how about that...). But we also have to properly evaluate user input, or it could bite the product down the road."[48]

In an email dated November 16th of 2005, Raimo Sump of Ethicon's Device Development R&D division notified Dan Smith and multiple TVT-SECUR project members "we're going to take the low risk of just discussing the Design Validation Report and to approve it before the appropriate Design Review".[49]

Following this approval, Gary Borkes, Ethicon's Design Quality Engineer of Ethicon's Woldwide Qualtiy Engineering, sent an email to Ethicon's Development Engineer, Raimo Sumps, Dan Smith, Martin Weisberg, and numerous members of the TVT-SECUR project team regarding his findings and concerns.[50] His comments were numerous and included:

> "I also think there are some concerns that could be scrutinized if used for the submission or in future audits, particularly with a study that had so many issues"

[48] ETH.MESH.05559108
[49] ETH.MESH.05559907
[50] ETH.MESH.05559905

"Calling a last minute design review with just team member and an independent observer to jump over the hurdle might no be the optimal approach with a study of such importance or having so many bumps (by the way, that is not just me talking)".

"I left Dan a number of voice mail messages an you gents an email before I was shut down". "My recommendation to Dan in my voicemails was that a formal design review be held to review the results prior to finalizing the report and prior to making a key submission. This review should include key management reps (Directors from all the key functional groups) to review the issues with the study, make them clearly aware, and have them buy in to the results and the direction".

"The study has a number of issues , including design needs not being met and lost documentation".

"it indicates that the release wire was pulled too hard by the users, causing a problem. This goes back to the issue we discussed at the previous design review about quantifying requirements. How much is too hard? What force does the release wire need to move at and withstand? If that hasn't been specified, then how can the corrective process actions of an assembly tool be confirmed".

"I agree with you – working in a hurry leads to mistakes".

Showing a callous disregard for the safety of patients, Ethicon employee, Mr. Sump, responded: "Yes, your comments are welcome but not all the time, up to months after lots of people spent a lot of work and effort to make the shit done, whether its in good shape or not". Dan Smith, TVT-SECUR project lead, responded, "Are you saying

you are not signing the Design Validation document before a formal design review can be set up? If so, we are out into December and this is now a huge set back".[51]

On November 18th of 2005, several Ethicon employees, including Mark Yale, discussed in an email the various flaws and issues in the design validation studies. Mark Yale indicated that there was "immense political pressure here and I need to actively manage the overall QE response….Bottom line if there is big steaming pile here (as I suspect), I need to know ASAP and push back hard on whomever to fix."[52]

On November 28th of 2005, a committee reviewed the report. The transcribed minutes of the meeting note that, although the report had been available for almost a week, the members were only emailed the report the night before the meeting, which did not provide the committee members with adequate time to review the Design Validation Report. It was felt that it would be more appropriate to provide all documents in advance rather than providing the report the night before the Design Review meeting. .[53] Furthermore, the committee members indicated that they could not conclude that the report related to design validation and that the report should be rewritten, "The goal of the rewritten report is to keep all important information but to point out clearly in the beginning when the design validation was successful and to discuss all issues and their planned or performed corrective actions in the end". The committee noted that, after reviewing the rewritten report, it would find a conclusion on how to proceed, "meaning the Design Validation succeeded as it is or the team has to make a complete or partly revalidation or addition some adding some more tests as Design Verification, respectively engineering tests."

[51] ETH.MESH.00526116
[52] ETH.MESH.00326211
[53] ETH.MESH.05616189

On December 20th of 2005, ten days after the completion of the Design Validation report reviewed herein, Ethicon's World Wide Director of Risk Management stepped in. Mark Yale emailed the TVT-SECUR project team indicating that he had reviewed the TVT-SECUR project, stating:

> "In light of this review, I have concerns with the recent TVT Secur design validation studies. Based on these concerns, I think the only path forward is to repeat the final study. While absolutely recognizing impact this has on timelines, I have a solid and defendable rationale for this decision".
>
> "TVT is one of the FDA focus devices. The September 2005 FDA was directed to TVT and MDR reportable events. We did cover design validation as part of this audit. It is fully expected that as some point in the future, the TVT Secur project will be reviewed by the FDA in detail and we will need to defend the clarity of our documentation and defend that we followed procedures in it's execution".
>
> "Additionally as you all may know we have ongoing issues with PROCEED mesh in the field, these issues have raised organizational awareness that we may not have correct balance between our need for speed to market and getting this done right before we release".
>
> "For the third amendment, the study was executed prior to all signatures being on the study protocol and without the product having gone through PR563 release. Both of these are non compliance with our procedures".
>
> "Speed is never a defendable excuse upon audit for non compliance. We must have a study done cleanly where the protocol is fully signed before study begins and the product is released via PR563. While recognizing this was a cadaver study and not true study in humans, the intent and spirit of PR563 is that it is how we control the release of clinical/design validation samples".

> "Design validation protocol has had three amendments written to it. this have come due to issues with each execution and amendments were done to correct, upon an audit this approach unfortunately looks like test till you get it right and is almost never cleanly defendable. Preferred approach is always to close out a study, and then move to another separate study to correct issues if necessary".
>
> "I have discussed this with Cindy Crosby and from a compliance position she is in absolute agreement that we need to conduct new study to correct these issues".[54]

In 2007, during the second year of worldwide TVT-SECUR use, Ethicon indicated that it would use the Australian surgeons as part of "design validation" for new training materials.[55] As discussed above, the design validation studies by Ethicon were significantly flawed as evidenced by Ethicon's own internal documents and the fact that Ethicon continued to conduct "design validations" in Australia two years after the product was launched worldwide.

This is inappropriate. To ensure patient safety, medical devices – and in particular those like TVT-SECUR that are intended as permanent implantable medical devices – must undergo design validation before launching the product, not two years after it is placed on the market and being implanted in women worldwide.

Summary of the TVT-SECUR Design Validation

Although product design problems and label problems were clearly identified in at least 25% of attempted cadaveric surgeries, Ethicon opted not to validate that its interventions corrected the problems. As noted herein, a problem that occurs 25% of the time is not proven resolved by three events without a problem. Furthermore, the design of the validation study was flawed in such a way that it was incapable of validating the

[54] ETH.MESH.03647753
[55] TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770

IFU label. The thirteen surgeons who were to validate the design of the TVT-Secur label were contemporaneously trained with procedural videos from two cadaver labs and a 'Big Print" of "Key Procedure Steps Guide Line" and an Ethicon Representative or independent observer was allowed to clarify any information shown in any of these labels.[56] The Design Validation report confirms that it was not included in the IFU, "The Key Procedural Guidelines document is not a controlled document and does not take the place of the IFU". A Design Validation lab must utilize the intended customer (surgeon). Ethicon chose to use some of the world's most experienced TVT surgeons, a group not representative of the intended customer. Additionally, Ethicon's internal documents demonstrate its awareness of a defective design validation.

Summary Opinion of Design Validation

It is my opinion to a reasonable degree of medical and professional certainty, as both a medical and medical device industry expert, that:

- Ethicon's design validation study failed to achieve its intended purpose, validation of the TVT-SECURdesign and IFU.
- A successful Design Validation is an internationally excepted requirement to commercialization.
- Ethicon's Design Validation Study demonstrated substantial design problems that were not remedied and resulted in injury to women.
- Ethicon knowingly compromised the device validation process, was aware of failures of validation, and knowingly opted not to repeat the design validation process to validate the design.

[56] ETH.MESH.00325954

Ethicon's internal company documents concerning its design validation demonstrate that the design validation was flawed, at least in part, because Ethicon rushed the TVT-SECUR to the market out of its inappropriate concern to recapture and/or retain its market share, as designed throughout this monograph. This placed patients at risk of suffering significant, unreasonable and unnecessary harms and, as a result thereof, women around the world were injured unnecessarily.

The Rush to Market and Unwillingness to Remove From Market

In 2004, in a document petitioning for the approval of the TVT-SECUR project, Project Leader and TVT-SECUR inventor, Dan Smith, stated "This project will be executed slightly differently to ensure marketing has clinical data at the planned launch". Mr. Smith also stated "Being first to market with a superior less-invasive TVT product and protecting our market share could be priceless". As will be described in the following paragraphs, his second goal took priority and lead to an abandonment of the first goal, clinical data.

In 2005, prior to a design freeze, Ethicon indicated that it planned to release the TVT-SECUR to market within three months of starting the first human trial.[57] Ethicon indicated that it needed the TVT-SECUR device in order to recapture its dwindling market share and maintain its revenue. It planned on charging a 15% premium (compared to its existing sling products).

Ethicon created a marketing strategy that would allow it sell its experimental TVT-SECUR device and implant TVT-SECUR in women prior to the demonstration of safety and efficacy. "The targeting strategy for TVTx (TVT-SECUR) is to aggressively cannibalize our existing TVT-O users followed by competitor obturator users in the first

[57] ETH.MESH.02248848

phase. This segment is the early adopters they do not require clinical data unlike the current classic users who have not adopted obturator because of lack of clinical data". [58]

In June of 2006, approximately three months prior to the market launch of the experimental TVT-SECUR device, Worldwide Group Marketing Director at Johnson & Johnson (Ethicon Inc), Harel Gadot notified Allison Brown, , Ethicon's Women's Health and Urology World Wide Marketing Director, of his concerns regarding Ethicon's plan to cancel randomized controlled trials.[59] Mr. Gadot noted that two of Ethicon's most important European Key Opinion Leaders, Professors Nilsson and Artibani, were quite concerned about a product launch prior to an RCT. He indicated that Dr. Artibani was supprised that "*we did not learn our lesson from the launch of MoniTorr*". He went on to describe how both KOL's were satisfied once they were informed of the RCT plan. He closed his email by noting his concern, *"I'm a bit concern that by canceling the RCT we will hurt our image in their eyes, especially after we've communicated this to them and worked with them to resolve any concerns they had associating with TVT SECUR. I believe that the success of the launch of TVT SECUR across EMEA (and probably other parts WW) will depend heavily on those two KOL and their willingness to assist us with our future communication plans. Therefore I would strongly recommend to find a way not to cancel completely the proposed RCT". As noted later in this chapter, the RCT plan would be cancelled.*

In 2006, Ethicon's paid consultant and Key Opinion leader, Professor Folke Flam, declined an invitation from Ethicon Israel, to provide educational training on the TVT-SECUR device stating, "Concerning TVT-SECUR, I have begun to realize (after workshops) that the product needs to be adjusted before I am willing to demonstrate it. As it is now there are some defects that have to be attended to. Thus, it would be better

[58] ETH.MESH.07898866

[59] ETH.MESH.01782851

for me to come when TVT SECUR is improved.[60] Ethicon's Worldwide Medical Director, David Robinson was copied forwarded this email.

A confidential internal document from May of 2007 reveals that Ethicon was aware of the inferiority of the TVT-SECUR device.[61] Some of the most experienced European surgeons were reporting 30-50 failure rates. Ethicon's Worldwide Director of Medical Affairs report on the European Experience noted "Key Experts are abandoning the procedure".

Ethicon's internal documents indicate that the TVT-S product was launched in the U.S. and Europe with only five weeks of uncontrolled human data[62].

Ethicon planned a 12-month clinical trial on 72 patients treated with the TVT-SECUR "U" and "Hammock" approaches.[63] However, at the time of launch, Ethicon only had 5-week-interim data on just 31 patients.

Just prior to device launch, Ethicon reviewed the five-week data from the first and only human trial.[64] This data was on a total of 31 women undergoing either a "Hammock" method TVT-S or a "U" method TVT-S by six of Ethicon's most experienced TVT surgeons. The raw data, shown in Ethicon's confidential "Interim Statistical Analysis Report" was available in May of 2006. The Confidential report was published on September 12th of 2006, approximately one week before Ethicon launched the TVT-SECURE to the public.[65]

Although 31 women had been implanted with the TVT-SECUR device, five week objective cure rates were available on 30 women. The objective cure rate was 66.7

[60] ETH.MESH.06893564
[61] TVT Secure: European Feedback presentation of Axel Arnaud M.D.
[62] ETH.MESH.03235997
[63] Referred to herein as "The First Human Use Study".
[64] Referred to herein as "Interim Data from the First Human Use Study".
[65] ETH.MESH.04499687

percent. Ten of thirty women remained wet at time of cough stress test. This remarkably low five week cure rate was obtained by five of the world's most experienced TVT-SECUR surgeons. Of perhaps even greater concern was the dramatic failure rates seen with the "Hammock" method. Dr. Karram noted a 75% objective failure rate. Dr. Khandwal noted a 50% failure rate.

On Saturday August 26th of 2006, Dr. David Robinson, Ethicon's Worldwide Medical Affairs Director emailed Allison London Brown, Ethicon's Women's Health and Urology World Wide Marketing Director, indicating that he did not consider the five week data to be good, "I am not sure I agree the data looks good. You are talking about a 10% failure in the primary end point and 8/31 (25%) positive cough tests in our secondary endpoints".[66]

My own review of the data suggests that the failure rate was actually 33%, a number worse than the number that concerned Dr. Robinson. Dr. Robinson would subsequently testify that the objective five-week failure rate was indeed higher than 25% and that approximately 65% of women experienced complications.[67]

In summary, on or about September 20th of 2006, with only five-weeks of prospective data, data suggesting that some of the world's most experienced expert surgeons could not achieve acceptable success rates, data suggesting that some of the world's most experienced expert surgeons experienced high TVT-SECURE complication rates, Ethicon began to sell its experimental TVT-SECUR device as a permanent medical implant to women around the world. It would later be demonstrated that failures of TVT-

[66] ETH.MESH.06151983
[67] Deposition of Dr. David Robinson, 7/24/2013, at 166:12-168:07

S could increase as much as 5-fold over the first six months.[68] Ethicon's internal document indicates that the 6 and 12 month data was to be submitted to IUGA for presentation in 2008, it opted to keep the abysmal results confidential.

The experiment continued on women around the world. In November of 2006, abysmal results and the lack of clinical data caused Ethicon's Australian Medical Director and Managing Director to recommend removing TVT-SECUR from the Australian market.[69] However, Ethicon's Chairman and Worldwide Vice President of Quality Assurance and Regulatory Affairs expressed concerns in regard to how such withdrawal might affect the world market. On November 2nd of 2006 Johnson and Johnson (Ethicon) Australian and New Zealand Medical Director, Dr. Aran Maree, sent an email to multiple Ethicon employees including World Wide Medical Director David Robinson.[70] Dr. Maree communicated his concerns with regard to astounding TVT-SECUR failure rates in the hands of some of the world's most experienced TVT surgeons. He noted that all three had implanted approximated 20 TVT-SECUR devices. He noted that Dr. Marcus Carey, the inventor of Ethicon's PROSIMA device, following training by Ethicon's TVT-SECUR paid consultant and preceptor, Dr. Vince Lucente, has experienced a 40% failure rate. Dr. Maree noted that Professor Malcom Frazer, trained by Dr. Vince Lucente[71] on an improved method, was not experiencing a

[68] Tommaselli GA, Di Carlo C, D'Afierc A, Formisano C, Fabozzi A, Nappi C. Efficacy and safety of TVT-secure in the treatment of female stress urinary incontinence: a systematic review (Abstract number 867). Proceedingsofthe 41stAnnual Meetingofthe International Continence Society (ICS), 2011Aug 29 to Sept 2, Glasgow, Scotland. 2011.

[69] ETH.MESH.00326842; ETH.MESH.00326843

[70] ETH.MESH.00326842

[71] Internal Ethicon company documents show that Dr. Lucente continued to obtain very poor results in his own patients, with a 1 year success rate of only 38.5 percent. See e.g., ETH.MESH06861281

substantial improvement in efficacy.[72,73] Dr. Frazier reported a 65% failure rate. Dr. Maree concluded:

> We feel that withdrawing the product from the market here is currently the most appropriate action for Australia. We believe this to be appropriate until we are confident that a modified technique appropriately documented and tested by way of clinical study, can be taught to our surgeons and will lead to optimal patient outcomes with this product.

Ethicon's Australian Managing Director Robert Scherini responded by email stating:

> Given this fact and the clinical experience to date we have decided to cease marketing of TVT Secur in Australia and New Zealand pending our ability to create a sound program of preceptorships, obtaining the necessary clinical evidence and having what I would consider to be a solid program for launch.

However, Ethicon's Chairman, Sheri McCoy expressed concern about the worldwide effects of such a withdrawal from the Australian market: "I am concerned that by ceasing marketing it creates specific issues for us and may have broader implications beyond Australia and New Zealand."

Ethicon's Worldwide Vice President of Quality Assurance and Regulatory Affairs agreed: "Absolutely this could cause problems in other areas of the world."

In 2007, Mr. Maree noted, in an email to the Vice President of Strategic Medical Affairs, "*We will also need to check that new products, when either significantly modified*

[72] It should be noted that Ethicon's TVT-SECUR project lead and inventor Dan Smith attempted to minimize the negative reports of Professor Frazier. However, Australian Medical Director Aran Maree, aftrer speaking with Dr. Frazier for hours, informed Ethicon that he believed Mr. Smith's comments were misrepresentations of Dr. Frazier's experience and, as a result of Dan Smith's meeting with Dr. Frazier and Mr. Smith's provision of method modification, Dr. Frazier's subsequent two patients were suffering from complications. See ETH.MESH.00327061-063

[73] See also ETH.MESH.00327060 (Dr. Frazier told Ethicon in November of 2007, among other things, that the TVT-SECUR labeling is fundamentally misleading. Despite the problems with the SECUR labeling, Ethicon never revised it and continued to provide inadequate warnings and instructions to physicians).

from predecessors or which bring with them a substantially new technique, have adequate pre-market safety and efficacy clinical data to justify their launch". [74]

In July of 2009, Ethicon drafted its confidential report of the six and twelve month data of this first human trial, the continuation of the 5-week interim analysis presented at IUGA in 2007, "*Presentation of main analysis at Day 35 and follow-up analyses at Months 6 & 12*". As discussed in the 2009 Chapter of this report, although Ethicon amended the protocol in an attempt to achieve success, the study revealed that the TVT-SECUR failed to meet both its efficacy and safety endpoints. Ethicon concluded:

> Therefore the procedures were not successful according to the criteria set out in the protocol and amendments….Substantial effort has to be channeled into developing a design of the single-incision sling that facilitates a safer and easier insertion…[and] As long as complications occur at the rate seen in this study and invasiveness is not very much lower than with the traditional mid-urethra tension-free operations, the GYNECARE TVT-SECUR procedure cannot be recommended as a first line treatment for stress urinary incontinence.[75]

The last subject in this study completed their 12-month follow-up on December 21st of 2007. In complete disregard of its own study results, Ethicon hid what it had learned and continued encourage the implantation of its defective device into women around the world.

Two of the six of the original six Ethicon Key Opinion Leaders who conducted this first human trial would not support the device thereafter.[76]

It is my opinion to a reasonable degree of medical and professional certainty that:

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[74] ETH.MESH.00642331

[75] ETH.MESH.02916532-615

[76] Artibani and Nilsson, ETH.MESH.2105223

- Ethicon rushed the TVT-SECUR to the market without conducting adequate clinical trials prior to launch, placing patients at significant risk of suffering: unnecessary injuries, treatment failure, and reoperation to treat recurrent stress urinary incontinence.
- Ethicon placed the TVT-SECUR on the market with short-term clinical data that showed the TVT-SECUR lacked the required efficacy and safety to justify its use as a permanent medical device especially when there were various alternative products on the market with significantly higher safety and efficacy profiles. By doing so, Ethicon placed patients at significant risk of suffering: unnecessary injuries, treatment failure, and reoperation to treat recurrent stress urinary incontinence.
- Ethicon misrepresented the safety and efficacy of the TVT-SECUR to the medical community despite its own analysis of the First Human Use Study, placing patients at significant risk of suffering: unnecessary injuries, treatment failure, and reoperation to treat recurrent stress urinary incontinence.
- Ethicon failed to act as a reasonable and prudent manufacturer when it launched the device for worldwide use with data demonstrating poor safety and efficacy outcomes in patients treated with the device.
- Ethicon withheld important safety and efficacy data revealed in its own internal study thereby preventing the medical community from learning that TVT-SECUR was associated with unreasonably high rates of failure and complications and failed to disclose that Ethicon's own Key Opinion Leaders concluded that the

TVT-SECUR should not be used as first-line therapy to treat stress urinary incontinence over other safer alternatives that were already on the market.

In Ethicon's internal document, a document with a title that includes the phrase "Maximizing the Investment", it acknowledges that Ethicon launched its TVT-SECUR device with "No long term data to support launch" and although it had made a "Commitment to 6 investigators for a post-launch RCT", "Upon launch" there was a "Decision not to start the RCT (Budget Constrains)."[77,78] This same Ethicon internal document notes that such decision has resulted in "Noise around the launch with no clinical data" both "Internally/Externally" and that there was a "Demand internally and externally for data collection to support launch". Ethicon indicates that the solution to this problem would be its TVT WORLD registry, a method that would allow them to collect data without the risk of demonstrating the failure it found in its secret TVT-SECUR RCT (its first human trial). As discussed in my chapter TVT WORLD, a registry does not test any hypothesis, such as one of effectiveness. Hence, unlike Ethicon's first human trial, it would not be able to show effectiveness and would provide Ethicon with the ability to "spin" the data. Ethicon went on to prematurely terminate the TVT-WORLD registry secondary to "Significant cost savings versus original plan". Ethicon indicated that they would save $700,000 over the course of five years.

In an Ethicon's internal 2010 marketing document discusses Ethicon ability to affect a surgeon's choice of product with the use of sales representative and product

[77] ETH.MESH.00134794
[78] Compare with ETH.MESH.02248848 (Ethicon 2005 budget for TVT-SECUR was $800MM, mostly for marketing. No money was allocated to robust clinical studies).

training.[79] This same document notes that the physicians believed that Ethicon rushed to market with TVT-Secur, "To some, Ethicon is guilty of two cardinal sins relating to surgical products – A rush to market in the absence of sound data (TVT-Secur) and inadequate communication related to a product problem/recall (morcellator)." This document further noted the "Belief by many physicians that Ethicon rushed TVT-Secur to market in the absence of sound clinical data – Left physician customers vulnerable to inferior clinical outcomes (quite frequently mentioned in most markets)"[80]

Furthermore, this same document indicates that Ethicon was aware that specialist surgeons believed products were being inappropriately marketed to non-specialists, "Many highly trained sub-specialists (e.g., Urogynecologists) are reportedly concerned about the "breadth" of manufacturer marketing efforts for products related to procedures that are perceived as relatively complicated (e.g., mesh/kits for pelvic organ prolapse). These physicians feel that these products should be limited to the "experts" and attribute complications/negative outcomes to user error among OB/GYNs and Gynecologic Surgeons". This is particularly concerning as Dr. Brian Flynn, an Ethicon TVT-SECUR preceptor and expert witness opines that the TVT-SECUR device was designed specifically to cater to the needs of the non-expert surgeons in the community.[81]

Ethicon's internal document, TVT-SECUR Quality Board, noted "Consider not carrying out a first human use trial and launching a product at the same time.[82] "The learnings from a first human use trial should be gathered, digested, and the device / training adjusted accordingly before launch", which was not done prior to TVT-Secur launch. Once Ethicon realized there was an issue that required design validation, it opted

[79] ETH.MESH.03643186
[80] ETH.MESH.03643186
[81] TVT-SECUR expert opinion of Dr. Brian Flynn, wave 3, page 52
[82] TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770

to conduct such validation on the public rather than in an IDE or IRB approved investigation. In 2007 Ethicon reported "Need to keep product in market to train people" opting to use the Australian patients (through observations of results of Australian surgeons) for design validation, "Australian physicians part of "design validation" for all new training materials. Although this same documented indicated that, at least, they would stop training new surgeons until new material was available, there is no evidence that this occurred.

In 2008, Ethicon polled surgeons with regard to what they disliked about a new hybrid sling. Of the seven characteristics queried by Ethicon, the number one answer was "no multi-center clinical data to evaluate".[83] This same Ethicon internal document provides evidence of Ethicon's decision to rush to the TVT-SECUR to market without sufficient clinical testing:

> After our risky situation with SECUR and increased demand for at least one year data" and "After our Prosima experience demonstrating significant difference between results at the inventor's site and other excellent surgeon's sites…Are we willing to go to market with 12 months RCT data from only the inventor's site?

Summary Opinion of Ethicon's Timeline to Market Market and Refusal to Remove the Defective Product from the Market.

It is my opinion to a reasonable degree of medical and professional certainty that Ethicon:

- Planned on launching the TVT-SECUR device without sufficient safety and efficacy data;
- Launched the TVT-SECUR with data demonstrating its lack of efficacy and safety; and

[83] ETH.MESH.09951746

- As noted in the review of the literature that follows, this conduct resulted in the harm of thousands of women worldwide.
- Refused to withdraw its defective TVT SECUR from the market even though it was aware of its defectiveness and risk to women and that such refusal was predicated on financial gain
-

TVT-S PATENT HISTORY & DEVELOPMENT HISTORY

The TVT-SECUR Patent Portfolio vs. The Well Being of Women

In July of 2004 Ethicon filed a provisional patent application for a self anchoring medical implant for treating urinary incontinence.[84] The application described a single-incision sling with fixation ends (anchors). The fixation ends were described to have barbs or "finger portions" projecting from the main or "central body" of the fixation elements with the fixation element taking on an "arrow-head" configuration. In Figure X, taken from the provisional patent application, the fingers are represented by 24 and the overall arrow-head configuration of the fixation end is easily noted (the fixation end is represented by the not hatched portion of the drawing).

Ethicon informed the patent office that it expected "this particular shape" to "minimize backward slippage or forward sliding, after the implant is surgically implanted in the patient". Ethicon added that it was important for the fixation end (arrow-like anchor) to have sufficient stiffness such that the fingers (barbs) would continue to "protrude laterally" "without folding, during surgical implantation and positioning so as

[84] USPTO 60/591,648

to prevent or minimize slippage with respect to the surrounding tissue". Although Ethicon offered an alternative embodiment of the fixation end, a rectangle without barbs, Ethicon noted that the barbed ("arrow-head") finger projection embodiment was its preferred design for fixation. This preferred fixation design was clearly part of Ethicon's TVT-SECUR design input. Ethicon's first and only live animal testing of the TVT-SECUR design, utilized this "fingered" "arrow-head" fixation member. Ethicon requested of the USPTO that it be granted a device claim that included this preferred fingered fixation feature. Although Ethicon concluded (from this live animal lab) that this preferred design resulted in the desired and required resistance to pull-out, this design was discarded. The commercialized version of the TVT-SECUR, as discussed elsewhere in this monograph, would have no projections, no arrow-head configuration, and never be validated in an animal lab.

Ethicon described its fixation ends to be covered with bio-absorbable polymer, preferably its proprietary ETHISORB, stating that the material is highly porous, providing a large internal surface area for cell attachment. This was in direct contradiction to Ethicon's description of this material provided in its application for marketing clearance. Ethicon described this material to be "impermeable" and allowing "on-growth" (rather than ingrowth).[85] Ethicon further demonstrated the importance of in-growth by indicating that additional macroscopic holes would be created in the Ethisorb covered fixation ends "to facilitate in-growth of tissue through the fixation elements to cause fixation elements to further adhere to surrounding tissue". These holes, shown in Figure from the provisional patent application were not included in the commercialized TVT-SECUR device.

[85] K991413

Ethicon also described the preferred embodiment of its new sling device to be covered by a plastic sheath stating "A sheath may allow protection against contamination or damage". Ethicon requested of the USPTO that it be granted a claim that included this feature. Although all of Ethicon's commercialized sling products included such a sheath, Ethicon's commercialization of the device described herein would exclude this "preferred" feature.

Ethicon chose to make specific device claims that included:

- An implant for treating SUI comprised of an elongated tape with biocompatible fixation ends, such ends having a tissue adherence property greater than the tape and sufficient to prevent movement of the implant following implantation
- The same implant with implant being of a length sufficiently short to prevent exit from the abdominal wall or obturator foramen.
- The same implant with a sheath covering the tape
- The same implant with fixation ends that have multiple finger projections that are generally triangular shape.
- The same element with fixation made of Ethisorb or components of Ethisorb

Ethicon chose to make specific method claims that included:

- A method for surgically implanting and implant for SUI comprising implanting the device of the device claims around the urethra without existing the body

On July 20th of 2005 Ethicon submitted an application to the USPTO that claimed the benefit of its 2004 application.[86] This application added to the new claim requests.

[86] USPTO 60/700857

Ethicon made additional device claims that included:

- The implant claimed in its previous application with a length of 5-10 centimeters.
- The implant claimed in the previous application in which the claimed Ethisorb was specified as Ethisorb Dura Patch
- The implant claimed in the previous application with the previously described square (no finger) fixation ends
- A medical implant inserter with an implant holding wire-like element, penetrating tip and a cutting edge

Ethicon made additional method claims that included:

- A method for implanting a suburethral implant utilized the inserter claimed in the new device claims
- The method of implanting the device of the previous application without the limitation of not existing the skin.

Ethicon filed its utility patent application in 2005. This was published in 2006. A Patent was granted in October of 2007. The USPTO granted Ethicon claims that could protect:

- A medical implant inserter that has a penetrating tip with a cutting edge and a wire like holding element
- The implanter of the above claim holding a mesh implant with fixation ends. Said ends being more than twice as stiff as the intervening mesh.
- A method of implanting a suburethral implant comprised of biocompatible fixation elements, implanted with the claimed insertion device and ceasing to make adjustment once the inserters were removed.

The majority of the claims were dedicated to a the details of the insertion device, attachment of the implant to the inserter and removal of the implant from the inserter. The claims of the patent application filed in in September of 2007 and published in December of 2007 made both device and method claims for a device that represented what would be commercialized as the TVT-SECUR device and method.[87]

The application claimed an implant for the use in the treatment of stress urinary incontinence that included bioabsorbable fixation elements that had "tissue adherence property greater than that of the tape" and "substantially rectangular planar configuration without physical projections extending outward therefrom".[88] The physical projections (Christmas tree or barbs) that were taught in Ethicon's initial 2004 patent application were known in that art and could not have resulted in an independent claim granted by the patent office.

Coincident to the change in the teachings from the patent application of 2005 to which this was a continuation in part (CIP), Ethicon had removed the projection (barbs) from its TVT-SECUR prototype, TVTx.[89] It is unclear if the continuation in part was a result of changes made to the TVTx (TVT SECUR prototype) or if the changes made to the TVTx were a result of a need to create a proprietary fixation mechanism, a way to make money.

However, as centuries of data had validated the effectiveness of barbed anchors and Ethicon believed that its TVTx live sheep lab had validated the effectiveness of the TVTx barbed anchor, it is more likely than not that the removal of the barb was resultant

[87] USPTO application number 11/854,049
[88] USPTO application number 11/854,049
[89] USPTO application number 11/190,601

to the need for a proprietary fixation mechanism. This is further suggested by the fact that Ethicon's patent application CIP claimed its novel Ethisorb/PDS fleece as a fixation mechanism. This application also claimed the implant with the above independent claim measuring between 5 and 10 centimeters.

The application claimed an implant for the use in the treatment of stress urinary incontinence that included fixation elements fabricated from a composite material that included Ethicon's Ethisorb and PDS film. Should this claims herein requested by Ethicon be granted by the USPTO, Ethicon could only financially benefit from such claims if it knew, projection free, Ethisorb fleeced, fixation ends demonstrated a greater adherence property than the PROLENE sling.

It is interesting to note that although Ethicon never conducted a single pre-market human trial to demonstrate efficacy and safety of its experimental TVT-SECUR device, it conducted cadaver labs to demonstrate that its novel, no projection, Ethibond fleeced fixation ends had greater adherence property than the PROLENE sling (TVT and TVT-O). The cadaver labs failed to demonstrate this.

On November 20th of 2007 Ethicon was granted a patent that claimed an implant for the treatment of stress urinary incontinence that included bioabsorbable fixation elements that had "tissue adherence property greater than that of the tape".[90]

In October of 2009 the USPTO granted Ethicon a patent with claims requested in 2007.[91] These claims included a claim for fixation elements having a "tissue adherence property greater than that of the tape (sling)", not having projections (barbs), and covered

[90] US 7,297,102 B2
[91] US 7,601,118 B2

with a "fleece" material defined to include Ethicon's proprietary Ethisorb – PDS combination. These claims included a claim for the device of the previous claim that measured between 5 and 10 cm. The claims included a method claim for implantation of this device in to the "obturator tissue".

Summary of Ethicon's TVT-SECUR IP Pathway

In summary, in 2004 Ethicon submitted its first patent application in an attempt to create patent protection for its experimental sling, a sling it needed, as discussed elsewhere in this monograph, to reclaim market share and protect revenue. Ethicon initially claimed a sling that that was sheathed and would not exit the body. It taught a preferred anchoring mechanism that was like an arrow-head.

Although Ethicon believed it had demonstrated, in a live animal lab, that the "arrow-head" featured TVT-SECUR prototype had the desired resistance to pull-out, this mechanism was well described in the prior art. Ethicon opted to make no claim requests for this feature and removed it from its TVT-SECUR design. Ethicon was unable to convince the USPTO to grant it a claim for a sling that did not exit the body (this had already been described by at least one inventor, James Browning). Ethicon was however granted a dependent claim for its device that provided a length that was between 5 and 10 cm. Ultimately, Ethicon would achieve patent protection on a sling that was between 5 and 10 centimeters, with Ethisorb covered, non-barbed fixation end, that had adherence property greater than that of the tape, and an inserter device for the same.

The most detailed claims were for the inserter and included the cutting edge, penetrating tip, and complex attachment and release mechanism. A principle author of

this patent portfolio was Ethicon's TVT-SECUR project leader and engineer, Dan Smith. The internal documents and medical literature discussed in detail throughout this monograph demonstrate the defective nature of the fixation ends, the short length, the stiff laser cut mesh, and the sharp arrowhead inserter. These defects lead to both high failure and complication rates. The internal documents discussed elsewhere herein demonstrate Ethicon's unwillingness to make any corrections to the defects that would not be covered by their patent position.[92]

Summary Opinion of Ethicon's I.P. Pathway

It is my opinion to a reasonable degree of medical and professional certainty that:

- Ethicon knew of design features that would have improved efficacy and allowed for the discarding of design features that caused injury;
- Ethicon omitted such features in order to utilize features that would provide it with substantial financial benefit.;
- Ethicon placed its financial interests ahead of the wellbeing of women.

TVT-World

TVT-World-Wide Observational Registry for Long-Term Data

In November of 2006 Ethicon opted to begin a TVT Registry, "TVT-World". The registry design called for up to 5,000 women across 60 registered sites. The objective was stated as "to obtain long-term clinical and patient reported outcomes on the GYNECARE family of TVT systems" and "Objective effectiveness will be defined as a negative standing cough stress test at 12 months". It was further stipulated that assessments would continue up to five years. Ethicon's registry protocol noted "With 5000 patients we are at

[92] See ETH.MESH.04048515 and the chapter of the efficacy chapter of this monograph. The proposed corrections to key TVT-SECUR defects would be outside the protection of Ethicon patent claims.

least 99% certain of detecting an adverse event that occur in 0.1% of the population (over the duration of the registry)".

Unlike a clinical study that allows investigators to evaluate both safety and efficacy, a registry is not designed to establish safety and efficacy and is typically employed to observe outcomes after such has been demonstrated by randomized controlled trials. A registry typically uses observational methods to collect uniform data to evaluate "real –world" outcomes for a population defined by a diseases state (SUI). By way of example, a registry may be employed after safety and efficacy has already been established, for post-market surveillance. It is not a substitute for a RCT or any prospective controlled trial.

Ethicon's TVT-World protocol includes this interim analysis statement, "Since no hypothesis is being tested, there is no effect on sample size". Without a hypothesis, as is typical of a registry, Ethicon removed any possibility of demonstrating significance; a p-value could not be calculated. There was no risk of failure to meet a pre-defined success benchmark, a problem that plagued its PROFLIT device RCT. Furthermore, the registry model, a model that excludes any hypothesis, would allow Ethicon to "spin" the data. Indeed, in April of 2008, Ethicon's Clinical Director, Judith Guauld, sent an email to World Wide Medical Director David Robinson stating, "my concern with Dhinagar (Ethicon Great Britin) is his closeness to EU marketing and his constant wish to "spin" data e.g. TVT-World interim".[93]

[93] ETH.MESH.03086214

In 2011 Mr. Dhinagar Subramanian would be an author of the TVT-World manuscript, a manuscript that spun the data.[94] This is discussed, in detail, in the Review of the Medical Literature chapter of this monograph. Of additional note, in order to rapidly gain such "spinable" data on its experimental TVT-SECUR device, Ethicon violated a principle of a registry. It altered physician behavior by requiring the first 20 cases at each site to use its experimental TVT-SECUR device.

Although the registry was set up to capture 5,000 procedures, a number it indicated was necessary to capture adverse events, it terminated the registry prematurely. In 2009 the TVT-World registry was terminated at 1,367 procedures. Ethicon also noted that patient follow-up would not be the projected five years but "patient follow-up will be reduced to one year".[95] Ethicon's reasons for prematurely terminating the registry included, "Internal resources are required to work on the new female SUI projects within our R&D pipeline (projects aimed at mitigating TVT-SECUR problems)" and the "The depth of data already generated within the registry is substantial and will provide multiple publication opportunities over the next few years".[96]

However, internal emails demonstrate that just prior to terminating the TVT-World registry Dr. Piet Hinoul, Ethicon's Worldwide Medical Affairs Director EMEA, received a TVT-World AE report from Ethicon employee, Colin Urquhart. After analyzing the data, Dr. Hinoul responded "This is pretty awful. Obviously there are a lot of investigators who mistake an adverse outcome for an adverse event. Certain centres

[94] Tincello, Douglas G., Theunis Botha, Douglas Grier, Peter Jones, Dhinagar Subramanian, Colin Urquhart, Aaron Kirkemo, and Salil Khandwala. "The TVT Worldwide Observational Registry for Long-Term Data: Safety and Efficacy of Suburethral Sling Insertion Approaches for Stress Urinary Incontinence in Women." *The Journal of Urology* 186.6 (2011): 2310-315
[95] ETH.MESH.03208952
[96] ETH.MESH.03208953

have a very high erosion rate it appears for continence tapes. I would not ask the investigators if they would [change], tell them you will change unless they object." [97]

Summary of TVT-World Registry

In summary, the TVT-SECUR world registry was a bastardized registry that appears to have been created to generate rapid data to be used for marketing purposes. AE reports showed that centres were reporting high erosion rates. The study was terminated prematurely and Ethicon's employee and co-author of TVT-World publication was accused of spinning the TVT-World data. It is my opinion to a reasonable degree of medical and professional certainty, that it is never appropriate to spin safety or efficacy data. By doing so, Ethicon continued to conceal important safety and efficacy data from physicians, placing patients at significant risk of suffering severe complications.

Review of The Medical Literature and Related Material

2003

In or about 2003 I was hired by Gyne Ideas, a start-up medical device company from the United Kingdom, to perform an evaluation of their recently cleared single incision sling. Inventor and gynecologic surgeon James Browning developed this sling in 2001.[98] The FDA cleared this single incision sling in 2003. I was subsequently hired to perform a case series and present my results, on behalf of Gyne Ideas, to C.R. Bard. C.R. Bard was considering the purchase of this device from Gyne Ideas. This represented the first U.S. implantations of a single incision midurethral sling. My case series yielded disappointing results. Efficacy was approximately 60% at three months. C.R. Bard opted not to purchase this property from Gyne Ideas.

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[97] ETH.MESH.03208548
[98] US6960160B2

2006

My Improvement on the minisling: Between 2006 and 2007 I worked with may engineer to improve the minisling. This work was done under an agreement with a company out of Scotland, Mpathy Medical. I invented a method that replaced the dangerous anchors of minislings with a rapidly absorbed suture. This suture removed the two main defects that caused minislings to fail, early migration and incorrect tensioning. The sutures were fixed at the level of the skin by means of a proprietary adjustable tiny bandage. The suture could be used for adjustment of sling tension for up to 72 hours. Over the course of the year, I performed approximately fifty adjustable stabilized minislings. Subjective and objective cure rates (after the first five cases) were 100%. Mpathy stated they would not be able to successfully protect their product from competition without a proprietary anchor. They also stated, "Doctors will just cut mesh and tie a suture on". They told me that we (my engineer and I) needed to put a hole in the tip of the absorbable anchor and attach the suture through this hole. They told me "We need to have a message that the anchor is essential" (See IMAGES 1,2,3). I performed approximately ten cases with this modification. Adjustability was substantially reduced, bleeding was increased, and several failures were noted.

2007

IUGA 32RD ANNUAL MEATING, Mexico,

Int Urogynecol J (2007) 18 (Suppl 1):S1–S24

Dr. Karam and Lucente presented their Ethicon Sponsored five-week follow-up TVT-S prospective observational data, An Evaluation Of The Gynecare Tvt Secur.[99]

[99] Karram, M; Lucente, V; Khandwala, S; Nilsson, C; Artibani, W; Dmochowski, An Evaluation Of The Gynecare Tvt Secur* System (Tension-Free Support For Incontinence) For The Treatment Of Stress Urinary Incontinence. Int Urogynecol J (2007) 18 (Suppl 1):S1–S24

They reported a 75% cure rate (by supine cough test). There was a notable difference between methods with the failure rate of the H method being more than double that of the U method. Although this study was set up to capture data at 5 weeks, six months, and 12 months, only the five-week data noted herein was published, and it was not published until 2007. Although the protocol stipulated that all patients would be included for the evaluation of both safety and efficacy, Karram et al opted to exclude the first two implants performed by each surgeon from the efficacy assessment.[100] Correcting for this bias by carrying the last observation forward would result in a five week cure rate of 66%. This remarkably low cure rate was obtained by some of the most experienced implanter in the world. It should be noted that this 66% rate is the exact cure rate found by analyzing the interim data set.[101] Additionally, Karram et al reported a 1.6% incidence of bladder perforation and a 5% incidence of difficulty with insertion. The investigators noted "It is critical that the steps in the Instructions for Use be followed precisely".

Debodinance et al reported their two-month prospective observational findings on the TVT-S device.[102] These investigators reporting on forty women, noted cure rates between 64% and 82%. Women with mixed urinary incontinence were least likely to be cured (64%). These investigators noted, at two months, a 2.5% incidence or extrusion, a 5% incidence of banding, and a 17% incidence of "painful postoperative course". Additionally, they noted a 2.5% incidence of hemorrhage and a 2.5% incidence of inability to place the device.

[100] Karram et al, Int Urogynecol J (2007) 18 (Suppl 1):S1–S24, pg S3, ETH.MESH.03714390
[101] ETH.MESH.04499687
[102] Debodinance, P; Lagrange, E; Amblard, J; Jacquetin, B, TVT Secur : More And More Minimal Invasive-Preliminary Prospective Study On 40 Cases. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

Han et al reported one-month follow-up of thirty women treated with the TVT-S device.[103] The authors reported a 67% cure rate (by negative stress test) and concluded, "The one-month cure rate was rather low when compared to TVT and TVT-Obturator". These authors also note a 6.6% incidence of bladder injury.

Friedman presented his plan for analysis of his TVT-S vs TVT-O data.[104] Friedman reported that "virtually no scientific papers appeared in the literature" with regard to the efficacy of the TVT-S device.

Albrich et al reported on their experience treating 24 women with the TVT-S device.[105] Only 18 were available for a mean of 18 weeks. The authors reported a 83% cure rate (by stress test). The noted a 25 percent extrusion rate. They concluded "These preliminary short term outcomes require a greater number of patients and longer follow-up to elucidate the future place of this novel microinvasive anti-incontinence procedure".

Marsh et al reported on their six week follow-up of forty women treated with TVT-S.[106] They noted a 74% subjective cure rate. They also reported a 5% incidence of button holing and a 5% incidence of voiding dysfunction.

Martan et al reported on twenty-five women treated with the TVT-S device.[107] The time of follow-up was not noted. These authors performed ultrasound assessment of all failures and note all failures to be associated with folding of the sling. They reported a 4% incidence of extrusion.

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[103] Han, H.C., Shukiman, I., Lee, L.C., TVT Secur® In Treating Female Stress Urinary Incontinence : Early Experience. . Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

[104] Friedman, M. TVT-S Vs TVT-O : Randomized, Prospective Comparative Study Of Intraoperative Complications, Perioperative Morbidity And Short-Term. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

[105] Albrich, S; Naumann, G; Skala, C; Koelbl, H. TVT-Secur: A Novel Approach For The Treatment Of Female Genuine Stress Urinary Incontinence. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

[106] Marsh, F.A., Assassa, P., An Audit Of The Introduction Of TVT Secur In Clinical Practice. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

[107] Martan, A, Masata, J., Svabik, K., Initial Experience With TVT-Secur System Procedure And The Reason For Persistent Stress Urinary Incontinence. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

Neuman et al described their first 150 teaching cases of TVT-S in Israel.[108] The authors reported that failures were addressed by "applying minimal extra tension upon the mesh". The authors, who disclosed industry affiliation, reported a 97% success rate. They did not report the time of follow-up or their definition of success. Neuman was unable to achieve a statistically significant improvement in efficacy with his method.[109] Of note, Neuman's method would result in a remarkably high rate of de novo dyspareunia and other expert surgeons would be unable to validate Neuman's claim for increased efficacy.[110] Furthermore, Neuman's subsequent manuscripts would result in his conclusion that there was no time benefit associated with the TVT-S procedure, there was no efficacy benefit of the TVT-S device, there was a two week TVT-S benefit with regard to lower post-operative pain compared to the TVT-O device (pain that responded to NSAID therapy), and there an 8% TVT-S related incidence (vs 0% for TVT-O) of persistent dyspareunia requiring surgery. He also reported an 8% resurgery rate secondary to persistent dyspareunia.[111] Neuman would inform Ethicon that there was not a method solution to pain and erosion, "Dr. Neuman informed Ethicon "Most of the vaginal pain and lateral tape protrusion is caused by the increased tape stiffness - my feeling it is due to the laser cutting"[112]. The Neuman modification also was associated

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[108] Neuman, M, Shaare-Zedek, M.C., Training TVT Secur: The First 150 Teachin Operations. Int Urogynecol J (2007) 18 (Suppl1):S25–S105

[109] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

[110] Neuman et al, Original Article Transobturator vs Single-Incision Suburethral Mini-slings for Treatment of Female Stress Urinary Incontinence: Early Postoperative Pain and 3-Year Follow-up. Journal of Minimally Invasive Gynecology, Vol 18, No6 , ETH.MESH.01784428, TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770. See also ETH.MESH.00642325 (Email discussing product design and training issues, Ethicon employ Dr. Khoo acknowledges that if products are not properly rolled out and physicians adequately trained, patients end up getting "the short end of the stick"), ETH.MESH.00327062. As noted throughout this monograph, numerous KOLs were trained in the modified methods of the "Cookbook" that included the modifications of Neuman, yet they were unable to improve efficacy or decrease complications.

[111] Neuman M. Peri-operative complication and early follow-up with 100 TVT-SECUR procedures. J Minim Invasive Gynecol. 2008;15: 480–484.

[112] ETH.MESH.03923121

with a high rate of de novo urge symptoms. Ethicon Key Opinion later , Dr. Tommaselli, would later use Neuman's method in an RCT and was unable to achieve efficacy of the TVT-O device.[113]

Saltz et al, including industry affiliated authors, reported on their retrospective chart review of 77 women undergoing TVT-S implantation.[114] The reported a six-week 69% cure rate (they did not define how cure was determined). The authors reported a zero incidence of mesh extrusion. The authors further reported "There is a real learning curve as demonstrated by the improvement in outcomes seen over time".

2008

IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONS

Int Urogynecol J (2008) 19 (suppl 1)

In September of 2008 multiple investigators presented their findings on the TVT-S device. Roovers and co authors, including Ethicon's medical director Pete Hinoul, presented their results of their Ethicon sponsored six-month prospective evaluation of the TVT-S device. They found a 2% incidence of bladder perforation, a 2% incidence of retention, and only a 76% cure rate (compared to 76% TVT at two years). The authors

[113] Tommaselli GA, Di Carlo C, D'Afierc A, Formisano C, Fabozzi A, Nappi C. Efficacy and safety of TVT-secure in the treatment of female stress urinary incontinence: a systematic review (Abstract number 867). Proceedingsofthe 41stAnnual Meetingofthe International Continence Society (ICS), 2011Aug 29 to Sept 2, Glasgow, Scotland. 2011.

[114] Saltz, SM; Haff, R. E; Lucente, V.R., SHORT-TERM ASSESSMENT OF PATIENTS UNDERGOING THE NEW TENSION FREE VAGINAL TAPE: SECUR PROCEDURE FOR TREATMENT OF STRESS URINARY INCONTINENCE. Int Urogynecol J (2007) 18 (Suppl 1):S25–S105

advised against the use of TVT-S as a first choice for the surgical treatment of urinary incontinence until more data was available.[115]

In September of 2008, Barbancini et al presented the findings of their prospective one-year evaluation of the TVT-S device.[116] These authors noted 10% incidence of recurrent UTIs, an 8% incidence of recurrent urinary tract infections, a 4.5% incidence of hemorrhage (>500cc) and a 2% incidence of erosion. These authors also found subjective and objective cure rates of 78 and 81%. These authors noted that these rates were approximately 10% lower than cure rates reported for TVT. At this same meeting, Mota et al presented their six-month retrospective data on TVT-S with the hammock method.[117] Mota found only a 72% subjective cure rate. The cure rate for SUI was reduced to only 63.5% amongst women with pre-operative SUI and urge symptoms. They also noted a 27% incidence of de novo urge incontinence amongst those women with pre-operative urge symptoms.

Martan et al presented their prospective 6 month data.[118] They noted a objective cure rate of only 62% and an 8% incidence of erosion. The authors concluded "The tape used in the TVT-S procedure is less elastic than that used in the TVT or TVT-O procedure, so this tape must be slightly over-tightened, which means the tape is not tension- free. These steps are crucial for the curative effect".

Debodinance and authors including Lucot, Cosson, Villet, and Jacquetin (a group that included the inventor of TVM and some of the most experienced Ethicon KOL's in

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[115] Roovers J, van Dessel N, Vervest H, den Boon J, Milani F, Hinoul P
IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONS
Int Urogynecol J (2008) 19 (suppl 1)
[116] Meschia M, Barbacini P, Pifarotti P, Ambrogi V, Ricci L, Spreafico L., IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)
[117] Mota R, Mascarenhas T, Costa F, Rasteiro C, Duarte S, melo A IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)
[118] Martan A, Svabik K, Masata J, El-Haddad R, Koleska T, Pavlikova M
IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

the world) reported on their one year prospective observational study.[119] These authors reported one year efficacy ranging between 40% and 72% with almost 60% of patients lost to follow-up. The authors concluded "The result are less good than TVT or obturator route procedure".

Smith et al presented their industry funded two-year prospective observational study of the TVT-S device.[120] The authors pointed out there was "little published data with regard to the safety or efficacy of single incision mesh slings for USI". They noted that, one year earlier, at the 2007 annual IUGA meeting, the absence of a single abstract with greater than five months of TVT-S follow-up. Smith enrolled forty-two patients of which forty agreed to follow-up assessment. Cure was defined as less than a one gram weight increase on a one hour pad test (1cc/hr). Smith noted objective cure rates of 38% at one month and 31% at one year.

This same year, Sharifiaghdas et al reported objective cure rates (by one-hour pad test) of 75% (at 6 months) for both full length TVT and rectus fascia slings.[121] Smith et al concluded "The short segment tape has a substantially lower cure rate than reported for full length tapes such as the TVT and the cure rate rapidly declined over the two year follow up period, especially during the first six months". Of additional note, by two years, approximately 40% had additional surgery and there was 7.5% incidence of mesh extrusion.

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[119] Debodinance P, Lagrange E, Amblard J, Yahi H, Lucot J, Cosson M, Villet R, Jacquetin B IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

[120] Smith A, Hilton P, North C, Ali-Ross N. IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

[121] Sharifiaghdas, F., Mortazavi , N., Tension-Free Vaginal Tape and Autologous Rectus Fascia Pubovaginal Sling for the Treatment of Urinary Stress Incontinence: A Medium-Term Follow-Up. Med Princ Pract 2008;17:209–214

Dr. Vince Lucente, Ethicon key opinion leader, presented his video, TVT Secur Surgical Technique and Learning Tips and Tricks.[122] Dr. Lucente taught that his team had learned that modifications to the procedure that increased efficacy. The included minimal hydrodissection, limited periurethral dissection to the pubic rami, and the placement of the sling under greater tension "compared to its predecessors". Dr. Lucente also taught the use of the cough test both for initial adjustment and a repeat cough test for final adjustment. Dr. Lucente also offered findings from his retrospective chart review of seventy-seven patients. He reported a 69% cure rate at six weeks. Of additional note, Dr. Lucente presented an abstract one year earlier in which he stated "It is critical that the steps in the Instructions for Use be followed precisely".[123]

Neuman published his perspective observational case series on the TVT-S device.[124] Fifty patients underwent TVT-S placement according to the teachings of Ethicon. Following evaluation of the low efficacy and high complication rates, Neuman modified the procedure on the next fifty patients, "Hence, the surgical tunnels were made wider, deeper, and shorter; the inserters were separated properly from the tapes before withdrawal; and space was avoided between the tape and the urethra". Therapeutic failure was defined by patient subjective complaints of incontinence and "clinically confirmed" incontinence (not defined in manuscript). Failure at one month was 20% amongst women undergoing the Ethicon method and 8% amongst women implanted with the Neuman modified method. Although 12-month efficacy was reported

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[122] Lucente, V., van Raalte, H., Molden, S., TVT Secur Surgical Technique and Learning Tips and Tricks. IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

[123] Karram, M; Lucente, V; Khandwala, S; Nilsson, C; Artibani, W; Dmochowski, AN Evaluation Of The Gynecare Tvt Secur* System (Tension-Free Support For Incontinence) For The Treatment Of Stress Urinary Incontinence. Int Urogynecol J (2007) 18 (Suppl 1):S1–S24

[124] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

to have increased by 8 and 3% respectively, this was by telephone interview only. Neuman reported an overall complication rate of 64% with the Ethicon method and 26% with his modification (Vaginal wall penetrations, extrusions, obstruction, OAB, dyspareunia, hematoma, tape removal). This difference was statistically significant. Neuman reported a 10% incidence of mesh extrusion amongst those treated with the Ethicon method and a 0% incidence of extrusion with the Neuman modification.

Neuman reported an 8% incidence vaginal wall penetration (injury) with the Ethicon method and a 0% incidence with the Neuman modification. The Ethicon method was associated with a 4% incidence of obstruction requiring surgical intervention (0% for Neuman modification). The Neuman modification was associated with 10% increase in urge symptoms. De novo urgency and frequency increased from 18% to 28% and de novo urge incontinence increased from 10% to 20%. Neuman noted "No space should be permitted in between the urethra and the TVT-SECUR, differing from the TVT, to achieve the de sired therapeutic result.

The inserters, being more than twice as wide as TVT and TVT-obturator needles, necessitate wider tunnels, 12 mm at least, to permit smooth passage of the tape and inserter and to avoid gathering of vaginal skin, which may lead to vaginal wall penetration. The tunnel depth should not go beyond the bone edge to avoid damaging the tissue meant to hold the coated tape edge". These teaching did not appear in the TVT-S IFU. Neuman concluded that the TVT-SECUR was "associated with mild early safety and efficacy problems", that were "rectified" by his modification. Neuman also noted, "[T]he novel TVT-SECUR's actual place among TVT and TVT- related procedures should be determined with randomized prospective longitudinal comparisons".

Confounding factors taint the findings of Neuman.

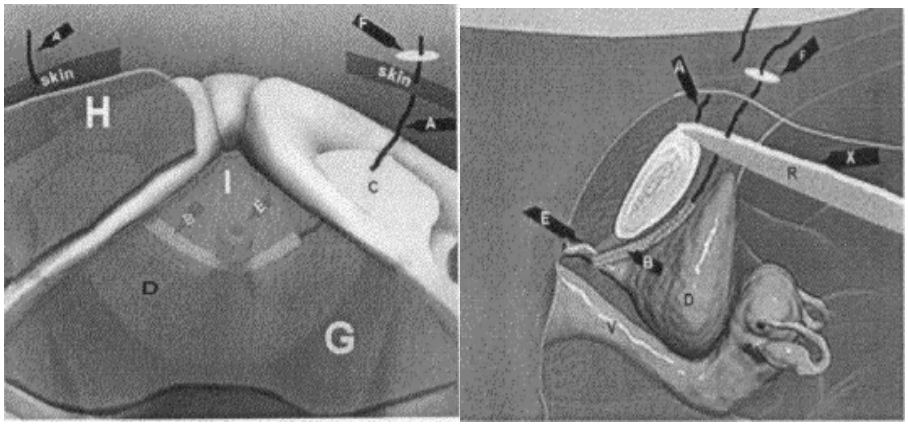
Over 70% of all subjects underwent concomitant procedures. Although Neuman reported that there was no statistically significant difference between the two groups, Neuman pooled anterior colporrhaphy, posterior colporrhaphy, and prolapse mesh implantation (did not evaluate group differences based on type of concomitant surgery). Hence, it is possible that differences between groups were secondary to concomitant surgery.

Of note, although the decrease in complications reported by Neuman, confounded as above, reached statistical significance, the improvement in efficacy did not. It should also be noted that any valid findings herein could only be generalized to the most experienced of TVT-S surgeons. By February of 2008, Neuman had implanted approximately 450 TVT-SECURdevices. It should also be noted that hundreds of patients were treated with the inferior method before Neuman learned his improved method. Of additional note, although Ethicon would include many Neuman modifications in its confidential cookbook and provide such in sporadic teachings, Ethicon never performed the RCT required to validate or invalidate the findings of Neuman. Of additional note, as discussed elsewhere in this monograph, neither other Key Opinion Leaders or the world of general gynecologists and urologists were able to reproduce the results of Neuman (which would later be shown to cause a high rate of dyspareunia).

Zipper. In or about 2008 I parted ways with Mpathy (secondary to a contract issues).[125] Later that year MPathy commercialized my method. That same year I filed a patent application for my method and my adjustable bandage.[126] My method eliminated

[125] On February 27th of 2008 I filed my invention with the USPTO. The following day, MPathy filed.
[126] US20090216072A1

many of the complications of the minislings including but not limited to the pain and bleeding associated with anchor penetration, resurgery secondary to failure, and obstruction from over-tensioning. As my method utilized the same surgical pathways and motions as existing retropubic and obturator slings, there was no learning curve (for the thousands of surgeons already familiar with these methods).



IMAGES 1& 2 :Zipper "Hammock" Method[127] Zipper "U" Method[128]

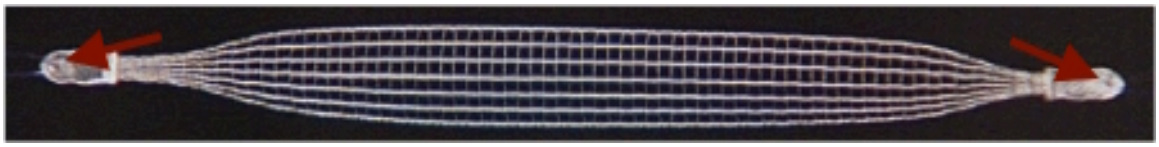


IMAGE 3: Holes Placed In original MPathy Minisling Anchors. Commercialized as Minitape®

National Institute for Health and Clinical Excellence (NICE)

Interventional procedure guidance 262 (2008)[129]

[127] US20090216072A1
[128] US20090216072A1

NICE is the independent organization responsible for providing evidence-based guidance on health and social care. In 2005 NICE merging with the Health Development Agency of the United Kingdom.

NICE creates guidelines with evidence-based recommendations on a wide range of topics in health, public health and social care. The nice charter includes the following narrative:

> NICE enables the NHS (National Health Service), local government and social care providers make the best use of resources by setting out the case for investment and disinvestment through our guidance programmes and other advice.
>
> Our guidance and other products are for the NHS, local authorities, social care organizations, charities and anyone with a responsibility for commissioning or providing healthcare, public health or social care services.
>
> All NICE committees are independent and unbiased. Once a topic has been referred to us by the Department of Health, or NHS England, neither organization has any more influence over the final guidance than any other stakeholder".
>
> Much of what NICE does has an impact on the healthcare industries that supply the NHS. We are very conscious of the responsibility we carry when we advise the NHS on the use of health technologies and we know that what we say about new technologies is often taken into account in health systems beyond the United Kingdom.
>
> None of our other guidance and products is subject to the same legal obligations as our technology appraisals and highly specialised technologies guidance. Nevertheless, health and social care professionals are actively encouraged to follow our recommendations to help them deliver the highest quality care.

In May of 2008 NICE published guidance on the use of Single Incision Slings, Single-incision sub-urethral short tape insertion for stress urinary incontinence in

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[129] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 262. Single-incision sub-urethral short tape insertion for stress urinary incontinence in women. May 2008. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG262

women.[130] The narrative noted that there was limited data on the procedure and described a 5% incidence of vaginal perforation, a 1-17% rate of erosion, and a 3-13% incidence of de novo urge symptoms. That guidance was as follows:

1. Current evidence on the safety and efficacy of single-incision sub-urethral short tape insertion for stress urinary incontinence in women is inadequate in quality and quantity. Therefore this procedure should be carried out only in the context of research studies or through submission of data to a national register (at the British Society of Urogynaecology [www.rcog.org.uk/bsug] or the Female and Reconstructive Urology Section of the British Association of Urological Surgeons [www.baus.org.uk])".
2. This procedure should only be carried out by a clinician with specific training in this technique.
3. Systematic long-term follow-up is essential. The Institute may review the procedure upon publication of further evidence.

Ethicon TVT-SECUR expert witness, Dr. Brian Flynn, values the opinions of NICE and cites NICE Guidelines to validate his opinions regarding the TVT and TVT-O devices.[131] The guidance document instructs healthcare providers:

> This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgment.
>
> Interventional procedures guidance is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland. This guidance is endorsed by NHS QIS for implementation by NHS Scotland.
>
> Interventional procedures guidance makes recommendations on the safety and efficacy of a procedure.

The document added the following guidance to patients:

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[130] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 262. Single-incision sub-urethral short tape insertion for stress urinary incontinence in women. May 2008. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG262

[131] TVT-Secur expert opinion of Dr. Brian Flynn pg 17

> NICE has produced information on this procedure for patients and their carers ('Understanding NICE guidance'). It explains the nature of the procedure and the decision made, and has been written with patient consent in mind.

In 2016 NICE would update their recommendation with deliberate exclusion of the the TVT-S data.

2009

In 2009 North et al published their prospective observational study of women undergoing implantation of the original, unmodified Minitape (without my modification).[132] Sixty women were implanted between 2002 and 2006. Two women declined all follow-up appointments. The cure rates (negative one hour pad test) were 33% at one month, 21% at six months, 16% at one year, and 10% at two years.

The authors utilized a last observation carried forward for these calculations. There was no substantial loss to follow-up noted at one month (3%). Efficacy at one month was 33%. Although subsequent loss to follow up creates a risk of bias, treating unknown data points as cures can compensate this for. This results in a two year cure of 40% (We know that 13 of the 19 seen at two years had failed. We know that 23 were excluded from two year analysis as had resurgery for failure. Hence, we no that 36 of the total recruited were have been uncured at two years. Thus, 24/60 or 40%, at most, could have been cured at two years).

North et al noted a 20% complication rate. There was 12% rate of mesh extrusion. There was an 8% incidence of pain requiring sling removal. The authors noted a 38%

[132] North, C., Hilton, P., Ali-Ross, N. and Smith, A. (2010), A 2-year observational study to determine the efficacy of a novel single incision sling procedure (Minitape™) for female stress urinary incontinence. BJOG: An International Journal of Obstetrics & Gynaecology, 117: 356–360.

incidence or repeat incontinence surgery and an overall rate of 45% rate of re-surgery (4 women for pain alone and 23 for SUI and other complications). Secondary to pain severe enough to cause removal, the authors subsequently debulked the Minitape anchors. Pain was not subsequently identified. North et al noted, "A larger study would be required to confirm the safety of the device, which is not appropriate given the level of efficacy demonstrated". The authors concluded, "Although it may not be appropriate to extrapolate the results from this study to all miniaturised versions of TVT, they do indicate that such new tapes should undergo robust clinical evaluation before they are used outside the clinical trial setting". This study was partially sponsored by the makers of the MiniTape, Mpathy Medical.

In 2009, Red Alinsod published on his experience with my modification to the original Mpathy minisling (commercialized at Minitape®).[133] Dr. Alinsod reported "The underlying hypothesis for a stabilized minisling is that it can produce the effectiveness of a full-length sling with the benefits of a minisling. It is proposed that minisling failure is a consequence of early sling slippage because the fixation means or anchors are embedded in indeterminate or poor tissue. By removing that possibility via stay suture stabilization for the critical 72 hours while early mesh invasion and fixation occur, position is maintained and good clinical outcomes ensue".

Dr. Alinsod reported 97% subjective cure rate (76 women treated with my method). This finding was similar to my own. Dr. Alinsod reported a 0% incidence of erosions with Minitape and a "near-zero" incidence when that same 19g/m^2 Smartmesh® was used for prolapse surgery. This was not consistent with my experience. I had noted a

[133] Alinsod, R., Recent Advances in Tape Slings for Female Urinary Stress Incontinence. Rev Obstet Gynecol. 2009;2(1):46-50.

2% incidence of erosion of the minisling and a 6% incidence or erosion with Smartmesh (used for prolapse surgery).

Dr. Alinsod pointed out that the Minitape was expected to be less traumatic than full length midurethral slings and was expected to avoid the neurologic complications of the obturator slings. Dr. Alinsod also cited a report of 60% TVT-SECUR efficacy.[134] This was consistent with my earlier findings of 60% efficacy for the MPathy minisling (prior to my modification). This 60% efficacy of the single incision sling would be validated by the 2014 Cochrane Group systematic review of the literature.[135] That same systematic review cited a 80-90% efficacy of full length midurethral slings.

Krofta et al[136] presented their one year prospective observational data on 73 women undergoing implantation of the TVT-S device. Objective cure was defined as the absence of SUI symptoms combined with a negative stress test. Ninety-one percent of cases were done under local anesthesia. The authors reported a 58% objective one-year cure rate. The authors reported a 6% incidence of mesh extrusion, an 11% incidence of repeat surgery for SUI within one year, a 23% incidence of de novo urge incontinence, and a 1% incidence or urethral erosion. The authors concluded, "TVT-S appears to be less effective than TVT or TOT for surgical treatment of stress urinary incontinence in women. There was a surprisingly high incidence of urge incontinence and mesh erosion".

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[134] Bacarat F, et al. Unfavorable immediate outcome of the TVT Secur sling in twenty consecutive women with stress urinary incontinence. Presented at: Annual Meeting of the American Urological Association; May 17-22, 2008; Orlando, FL.

[135] Nambiar A, Cody jD, jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Databaseof Systematic Reviews*2014, Issue 6. Art. No.: CD008709. DOl: 1O.1002/14651858.CD008709.pub2. "Women were more likely to remain incontinent after surgery with single-incision slings than with retropubic slings such as tension-free vaginal tape *(TVT)* (121/292, 41% vs 72/281, 26%; risk ratio (RR) 2.08, 95% confidence interval (CI) 1.04 to 4.14)"

[136] ETH.MESH.00274015

In 2009, Hubka et al published their cadaveric study, Anatomical relationship and fixation of tension-free vaginal tape Secur.[137] In their abstract, the authors noted "So far, there has not been any anatomical study focussed on TVT-S, so we decided to investigate anatomical localization, assess the safety of this method and examine the fixation site of the TVT-S tape in the light of reported haemorrhagic complication during TVT-S". In their study, Hubka et al placed TVT-S inserters bilaterally in 14 embalmed and five fresh frozen female bodies (Utilzing on the "H" method). They followed the teachings of Ethicon's TVT-S IFU. The authors noted that the surgeon implanting the TVT-S was experienced in the procedure.

The correct placement of the TVT-S inserter is into the obturator internus muscle. The authors defined correct placement (for this study) as any insertion deeper than 1mm into the obturator internus muscle. The authors defined acceptable placement as any placement through the obturator internus fascia but less than 1 mm into the obturator internus muscle. If the tip did not penetrate the obturator fascia, the insertion was considered an unacceptable placement. Amongst the embalmed cadavers, acceptable placement was noted in only 32% of insertions. Unacceptable placement was note in 46% of passes. The authors reported that correct placement occurred in 20% of fresh cadavers cases and incorrect placement occurred in 60% of fresh cadaver cases.

The authors reported that the introducer was a mean of 2.63 cm from the obturator nerve (they used the nerve as the measuring point for the obturator bundle) on fresh cadavers. Although the mean for embalmed cadavers was a bit higher, one trajectory was only 0.67 cm from the obturator nerve (and perhaps closer to the vessels). The authors

[137] Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88.

also noted that the tip of the introducer was approximately 5 mm from the blood supply of the obturator muscle. They do not provide a range or mean for this measurement. The experienced TVT-S surgeon performing these cases entered the bladder in 10% of passes. This finding was absent from cadaveric studies of other slings including that of Hinoul et al.[138] They authors stated that hip flexion, 90 vs 60 degrees did not significantly effect placement of the introducer.

Although the authors concluded that they had "established that TVT-S minimally endangers the obturator bundle and that the position of fixation does not change significantly with changing the position of the legs from 90° to 60°. Neither of these statements are correct. As noted herein, this cadaveric surgery was done by a surgeon experienced in the TVT-S procedure. This experienced surgeon, without and abscuration of bleeding, came within 0.67 cm of the obturator nerve. The TVT-S tape is wider than 0.67 cm. The investigators used the same cadaver for the 90° to 60° hip flexion insertions.

Hence, it is more likely than not that the track created by the first insertion was followed (at least in part) by the second insertions. No conclusions, with regard to hip flexion, can be made. Hinoul et al had previously demonstrated the effects of hip flexion on insertion, demonstrating a hip flexion of less than 80 degrees was dangerous. The importance of flexion beyond 80 degrees was noted in the TVT-S method of Neuman and

[138] Hinoul P, Vanormelingen L, Roovers JP, de Jonge E, Smajda S (2007) Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O). Int Urogynecol J Pelvic Floor Dysfunct 18:1201–1206

memorialized in the internal documents of Ethicon.[139] Ethicon did not teach hip flexion in its TVT-S IFU.[140]

Hubka et al concluded that the TVT-S introducer was capable of causing hemorrhage by injuring the blood supply to the obturator internus muscle, "As we have documented, haemorrhagic complication can be caused by the nutritive artery of the obturator internus muscle". A surgeon experienced in the TVT-S procedure demonstrated this finding. The authors stated they had proven "that the rate of correct placement is relatively poor in comparison with other TVT methods". They provided further validation of their findings by noting that "The success rate of fixation in the obturator internus muscle in this study is almost identical to our success rate of treatment in long-term follow-up after the TVT-S procedure (62%)".[141] They concluded, "The course of the inserter is less often confined within the body of the obturator internus muscle than anticipated by the manufacturer, and it often penetrates into the lesser pelvis, thus risking visceral injury".

In July of 2009 Ethicon produced its confidential report of the six and twelve month data of its first human trial, the continuation of the 5-week interim analysis presented at IUGA in 2007, "*Presentation of main analysis at Day 35 and follow-up analyses at Months 6 & 12*".[142] This was a continuation of Ethicon's protocol that randomized patients to TVT-SECUR "U" and "Hammock" surgery. The surgery was

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[139] ETH.MESH.02320488

[140] Hinoul P, Vanormelingen L, Roovers JP, de Jonge E, Smajda S (2007) Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O). Int Urogynecol J Pelvic Floor Dysfunct 18:1201–1206

[141] Martan A, Svabik K, Masata J, El-Haddad R, Koleska T, Pavlikova M (2008) Initial experience with TVT-Secur system procedure. Int Urogynecol J Pelvic Floor Dysfunct 19(Suppl 1): S10–S11

[142] ETH.MESH.02916532-615

performed by some of the most experienced TVT surgeons in the world. The amended study protocol defined effectiveness as greater than 49% subjective improvement on a visual analog scale (changed from an objective cure criteria). The efficacy evaluation stipulated that the success, greater than 49% subjective improvement, must be noted in at least 80% of the study population. At 12 months analysis, both the "U" and "hammock" methods failed to meet the success criteria (success was 79% and 62% respectively). Of additional note, the six month analysis had already found the procedure to be a failure. Sixty-five percent of the patients experienced adverse events. Thirty-one percent experienced major device related complications. Ethicon's confidential documentation of this data notes that study failed to meet its safety success criteria.[143] Ethicon concluded "*Therefore the procedures were not successful according to the criteria set out in the protocol and amendments*", "*Substantial effort has to be channeled into developing a design of the single-incision sling that facilitates a safer and easier insertion*", and "*As long as complications occur at the rate seen in this study and invasiveness is not very much lower than with the traditional mid-urethra tension-free operations, the GYNECARE TVT-SECUR procedure cannot be recommended as a first line treatment for stress urinary incontinence*". One must consider that the horrible results of this confidential first human trial occurred in the hands of the best TVT implanters in the world and that such results were further biased as Ethicon excluded patients that were most likely to fail (women with low urethral closure pressures or low leak point pressures, those with pelvic organ prolapse beyond mild stage 2, and those with prior incontinence surgery). One need not be skilled in the art of surgery or statistics to consider what the results might have looked like if the surgeries had bee performed by average surgeons on patients that were not selected based on an increased likelihood of success.

[143] ETH.MESH,02916602

2010

In 2010 Cornu et al published their prospective observational study of 45 consecutive women undergoing implantation with the TVT-S device.[144] Four patients underwent concomitant PROLIFT implantation. All interventions were by the same surgeon. With cure defined as no pad usage, no stress related leakage (a stress-test was performed) and a Patient Global Impression of Improvement (PGI-I) scale score of one or two, cure at one month (with no loss to follow-up) was 60%. Thirteen percent were considered failures (not improved). By six months, 15% of cured women were no longer cured and failure had increased to 28%. At a mean final follow-up of 30.2 months, cure had decreased to 40% and failure had increased to 42% (no loss to follow-up). The authors reported an overall recurrence rate of 33% by time of last follow-up (mean 30.2 months). They reported a repeat incontinence surgery rate of 27%. No erosions were noted. The de novo urgency rate was 11%. The authors hypothesized that lower failure rates of previous studies were likely a result of their short follow-up. The authors also hypothesized the high failure rate may have been secondary to the self-fixing secure tip of the TVT-SECUR, "[S]ince it had not been evaluated yet in long-term studies. The system may not resist periurethral tissue modifications with time, and slip and lose its efficacy".

This is an interesting and insightful observation as the novel, experimental tips, were made of material Ethicon claimed was impervious and allowed ongrowth (not ingrowth). They added, "Our results should encourage authors who have presented large series based on short-term evaluation to present their results with updated follow-up".

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[144] Cornu, Jean-Nicolas, Philippe SÃ¨be, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, and Francois Haab. "Midterm Prospective Evaluation of TVT-Secur Reveals High Failure Rate." *European Urology* 58.1 (2010): 157-61.

Cornu et al concluded, "These results demonstrate the importance of a long follow-up when a new device is evaluated in the field of urinary incontinence. Indications of TVT-Secur for SUI in women should be reconsidered".

In 2010 Jeffrey et al presented their systematic review of the literature on minislings.[145] This abstract was presented at the annual ICS meeting and published in Neurourology and Urodynamics. The authors performed a meta-analysis of any study that "showed any relevance" to the topic of "mini-slings" and included studies on TVT-Secur, Miniarc, and Ajust. The date range is not disclosed. Fifty-seven studies were identified. Jeffrey noted "Despite the widespread use of these products, there is unfortunately limited data available on the efficacy and complications of these procedures". Consistent with this, eighty percent of the included studies were represented by only by published abstracts. Only 5% of the included studies were represented by randomized controlled trials. As Jeffrey had noted, limited data was available. Looking at the eleven papers that were published in peer reviewed journals, Jeffrey reported a 76% overall cure rate at a mean follow-up of nine months. In these papers, TVT-SECURdemonstrated a 73% objective and subjective cure rate at a mean follow-up of nine months. Jeffrey reported a 3% risk of TVT-Secur erosion, 6% incidence of de-novo urgency and 0.4% risk of bladder injury. The authors concluded, "In this systematic review, overall cure rates for the mini-slings appears to be lower than the reported rates reported for the retropubic and transobturator tapes. The complication rates, however, appear to be reduced when performing the mini-slings".

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[145] Jeffery S, Acharyya R, Algar M, Makhene M, Makhene M Mini-sling procedures in stress urinary incontinence: a systematic review of efficacy and complications (Abstract number 5). *Neurourology and Urodynamics 2010; 29(6):* 811- 2., and presented 8/25/10 at ICS annual meeting.

Although the authors' finding of poor efficacy was consistent with the findings of the literature of the time, their conclusion of "reduced complications" was not. In 2008 Mota et al reported a 22.5% incidence of de novo urgency and Neuman reported an 18% incidence of de novo urgency. In 2009 Krofta reported a 23% incidence of de novo urgency and noted that it was "surprisingly high". In 2007 Albrich noted a 25% incidence of erosion.

In 2008 Smith et al noted a 7.5% incidence of erosion and Neuman noted a 10% incidence of erosion. In 2009 Krofta noted a 6% incidence or erosion and North noted a 12% incidence of erosion. Although Jeffrey does not disclose the list of included and excluded studies, it appears that at least several studies with high complications rates were curiously excluded. To the extent that such studies were not excluded, it is curious that Jeffrey has opted not to comment on the high rate of complications noted in many studies. Furthermore, the mean follow-up of only nine months precludes any conclusions regarding complications beyond such time frame.

In summary, this meta-analysis is weakened by the extreme lack of randomized controlled studies and the exclusion of the list of included and excluded studies raises concern for bias. The findings of decreased efficacy of the TVT-SECUR would be validated by future RCTs and Meta-analysis. The finding of decreased complications would not be validated by future RCTs and Meta-analysis.

Tommasselli et al published their manuscript of their prospective observational evaluation of the TVT-S and TVT-O devices.[146] Data was available for thirty-eight TVT-O subjects and thirty-seven TVT-S subjects. The authors state that the TVT-O was

[146] Tommaselli, G., Costantino, D. C., Gargano, V., Formisano, C., Scala, M., Nappi, C., Efficacy and safety of TVT-O and TVT-Secur in the treatment of female stress urinary incontinence: 1-year follow-up. Int Urogynecol J (2010) 21:1211–1217

implanted according to the technique described by Leval.[147] This technique differs from that taught by Ethicon. Leval described leaving a space between the sling and the urethra (described creating a ½ cm gap). The authors state that the TVT-S was implanted according to the hammock technique proposed by Neuman. This technique differs from that taught by Ethicon. Neuman taught making a wider submucosal dissection (12mm vs 10mm). Neuman taught greater tension ("space was avoided between the tape and urethra").[148] Tomesselli also stated that that they did not perforate the obturator membrane. Although it is unclear how they ensured such, the perforation of the obturator membrane is likely to occur under the teachings of Ethicon who taught "if contact with the bone is not made within 3 to 4 cm of advancement, STOP and reconfirm proper direction to the inferior edge of the pubic ramus prior to further insertion".[149]

All cases were done under spinal anesthesia, the exception rather than the rule for slings performed in the United States. A single surgeon who had already performed more than fifty of each procedure did all cases.

Tommasselli reported TVT-S and TVT-O to be associated with 81% and 83% objective cure rates. The authors do not state if these are one, six, or twelve month cures. The authors point out that these cure rates were not significantly different. The authors concluded, "both techniques appeared to be safe and effective in the surgical treatment of SUI. Both methods were considered satisfactory by the patients. TVT-Secur shortened

[147] de Leval J (2003) Novel surgincal technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol 44:724–730
[148] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484
[149] ETH.MESH.02340585

operative time and reduced bladder obstruction and thigh pain, though presenting higher de novo urgency rates. Pain scores resulted lower in TVT-Secur group, reflecting a less invasiveness".

The findings of this study do not apply to the TVT-S or TVT-O devices and procedures when implanted according to the labeled teachings of Ethicon. As noted above, the method described in this study were modified. With regard to the TVT-S procedure (peformed according to the method of Neuman), Tommasselli noted that their results may have differed from those of other investigators secondary to the method deviations in this study, "Indeed, Neuman suggested some modifications to improve the performances of this device. First, no space should be left between the tape and the urethra, since, differently from TVT-O, there is a better functional result. Second, since TVT-Secur introducers have bigger dimensions in comparison with TVT-O passers, periurethral tunnel must be wider, at least 12 mm, to allow an easy passage of the introducers and to avoid lesions to vaginal mucosa. Third, the depth of the periurethral tunnel must not go beyond the pubic bone, in order to avoid lesions to the tissue that must receive the extremity of the introducer, thus allowing the attachment of the device. Finally, the mechanism that holds the tip of the sling must be removed adequately to avoid inappropriate removal of sling. The adoption of these measures yielded an improvement of results in the application of TVT-Secur".

Additionally, it must be noted that Tommasselli chose to only evaluate pain at post-operative day one and one month (even though the study was designed to capture data to one year). Of yet further importance, the surgeon had performed at least fifty TVT-S procedures prior to this study. The number may have been in great excess of fifty.

The authors added, "Indeed, the present data allow us to calculate that in order to obtain the statistical power necessary to evaluate if TVT-Secur is as effective as TVT-O, considering as clinically relevant a difference of 5%, at least 350 patients per arm would be needed. This is approximately ten times the number evaluated herein. It should also be noted that the Cochrane group assessed this study and reported that "the risk of bias was considered high as a result of high drop out rates".

2011

Abdel-Fattah (2011)[150]

Single-Incision Mini-Slings Versus Standard Midurethral Slings in Surgical Management of Female Stress Urinary Incontinence: A Meta-Analysis of Effectiveness and Complications

Abdel-Fattah et al reported on their systematic review of the literature (from 1996 to January of 2011) for all randomized controlled trials (RCTs) comparing incision slings (SIS) to standard midurethral sling (SMUS). The authors stated that this was the first meta-analysis of RCTs to assess the efficacy and peri-operative morbidity of single incision slings versus standard midurethral slings. Nine RCTs with a mean follow-up of 9.5 months were included. The TVT-SECUR device was the studied SIS in approximately two-thirds of the RCTs (The TVT-S was implanted in 72% of the women in the SIS sling arms of the included studies). The authors found the single incision sling to be associated it a significantly lower subjective and objective cure rate as well as higher reoperation rates for SUI. The relative risk of repeat SUI surgery following SIS was almost seven fold that of standard midurethral slings. The relative risk of mesh

[150] Abdel-Fanah M, Ford JA, lim C P, Madhuvrata P., Single- Incision Mini-Slings Versus Standard Midurerthral Slings In Surgical Management Of Female Stress Urinary Incontinence: A Meta-Analysis Of Effectiveness And Complications. *European Urology.* 2011, 60(3),468-80.

erosion following SIS was almost four fold that of standard midurethral slings. The relative risk of de novo urgency following SIS was approximated double that of standard midurethral slings. The authors pointed out that not of the included studies assessed sexual function.

The authors pointed out that none of the include studies evaluated economic outcomes. They added, "However, it may be argued that in light of this meta-analysis finding of inferior patient- reported and objective cure rates in the SIMS group, health economic analysis may be of little significance". There was no significant difference in quality of life scores and "No studies reported duration of time required to return to normal activities/work.

The authors found no significant difference in operative time when comparing SIS to TO SMUS. When comparing SIS to RP SMUS, the authors reported the SIS to be 8.67 minutes shorter (statistically significant). The authors reported the SIS to be associated with lower post-operative day one pain scores compared to the obturator MUS. They authors added that no studies showed that a reduction in postoperative pain resulted in a significant QOL benefit. Data was insufficient to evaluate pain beyond post-operative day number one. The authors reported less groin pain when comparing SIS to obturator MUS.

This group of authors, lead by a principle author who was an industry preceptor for the SIS, noted that the growing use of SIS was "proceeding in advance of any supporting high quality data" and "[R]CTs with long-term follow-up are crucial if we are to know the durability and long-term morbidity of our surgical interventions. We recommend the initiation of an adequately powered and properly designed RCT to

compare the new adjustable SIMS with SMUS with long-term follow-up and health economic analysis. Until then SIMS should be performed only within a research context". They concluded, "This current evidence applies only to the types of SIMS included in the meta-analysis and does not support their use in clinical practice". Seventy percent of the women in this analysis were treated with TVT-SECUR.

Tommaselli (2011)[151]

Tommaselli et al reported their retrospective chart review of 68 women who had been implanted with the TVT-S device by means of the method "H" method of Neuman. All surgeries were performed by Dr. Tommaselli. The first ten cases were excluded. The authors reported an 81% cure rate at 24 months (negative CST and urodynamic test). Tommaselli et al noted a five fold increase in the failure rate between one month and 6 months (2 patients had persistent incontinence noted at one month and another 11 had recurred by six months). The authors noted that an additional 2.9% failed between six months and twenty-four months (2.9% failed by one month, an additional 16.2% failed by 6 six months, and another 2.9 percent by 24 months). There was a significant increase in the fear of incontinence. There was a significant increase in coital incontinence. There was an increase in dyspareunia that did not reach statistical significance. Although the authors state that 62% of women were sexually active, they do not state how many were sexually active prior to the implantation of the TVT-S device. Pain scores were zero at six months, 12 months and 24 months. There was one case of hemorrhage and one re-surgery for sling excision secondary to retention.

[151] Tommaselli GA, Di Carlo C, D'Afierc A, Formisano C, Fabozzi A, Nappi C. Efficacy and safety of TVT-secure in the treatment of female stress urinary incontinence: a systematic review (Abstract number 867). Proceedingsofthe 41stAnnual Meetingofthe International Continence Society (ICS), 2011Aug 29 to Sept 2, Glasgow, Scotland. 2011.

Although Tommaselli et al stated that the procedure had no negative impact on sexual function; they therein ignored the significant increase in coital incontinence and the trend toward increased dyspareunia. Although ultrasound evaluation demonstrated that the sling was maintained in the correct position, strangely, the authors only performed ultrasound in the continent patients. This is quiet odd and without explanation.

The authors noted that the objective cure rate was lower than that of the TVT-O as reported in the literature. The offered, "Indeed, anatomical studies have shown that the lateral end of the TVT-S tape were placed in an acceptable position in only 53.6 % of cases using the H approach. It seems that the positioning of TVT-Secur is highly variable and the standardization of the technique may not be easily achieved". They concluded, "Since it involves procedural passages that may worsen its outcomes and since standardization is difficult, it should be limited to previously untreated patients affected by mild or moderate isolated SUI".

In summary, Tommaselli et al reported a cure rate that they believed to be less than that of TVT-O, noted a rapid fall of in cures during the first six months, noted a significant adverse effect on sexual function, and attributed the high failure rate to methodological problems. It should be noted that the risk of selection bias was high as this is a retrospective analysis. We do not have any information on the number of patients who were not available for 24-month analysis or the status of those patients at earlier times (e.g. Many patients could have failed at six months and been lost to follow-up. As noted, failure rate is high in the first six months).

Neuman (2011)[152]

Transobturator vs Single-Incision Suburethral Mini-slings for Treatment of Female Stress Urinary Incontinence: Early Postoperative Pain and 3-Year Follow-up[153]

In 2011 Neuman et al published the findings of their non-randomized prospective evaluation comparing TVT-Secur and TVT-O devices. The TVT-S device was not implanted in accordance with the IFU but rather with the technique described by Neuman.[154] A total of 73 and 79 women were implanted with the TVT-O and S devices. A total of 69 and 77 were available for follow-up a three years. Neuman et al found no difference in cure rates between the two procedures (87 and 90%). Although the authors identified a higher incidence operative vaginal and thigh pain amongst the TVT-O patients (32% vs 1%), this finding was transient, noted only in the initial two weeks following surgery. In contrast to the transient postoperative pain, de-novo dyspareunia amongst TVT-SECUR patients was not transient, and occurred only amongst women in the TVT-SECUR group, "De novo dyspareunia occurred only in women who underwent the TVT-SECUR (5 of 77 patients; 7.9% vs 0%) and was not self-limited. The authors concluded that the TVT-O and TVT-S procedures had satisfactory cure rates and low complication rates, that sexually inactive women might benefit from the TVT-S secondary to the lower incidence of pain during the first two weeks following surgery, and that sexually active women might prefer TVT-O over TVT-S because of the lower rate of dyspareunia. It is unclear how or why the authors would consider the

[152] Neuman, Menahem, Vladimir Sosnovski, Mohammad Kais, Ella Ophir, and Jacob Bornstein. "Transobturator vs Single-Incision Suburethral Mini-slings for Treatment of Female Stress Urinary Incontinence: Early Postoperative Pain and 3-Year Follow-up." *Journal of Minimally Invasive Gynecology* 18.6 (2011): 769-73.

[153] Neuman, Menahem, Vladimir Sosnovski, Mohammad Kais, Ella Ophir, and Jacob Bornstein. "Transobturator vs Single-Incision Suburethral Mini-slings for Treatment of Female Stress Urinary Incontinence: Early Postoperative Pain and 3-Year Follow-up." *Journal of Minimally Invasive Gynecology* 18.6 (2011): 769-73.

[154] Neuman M. Peri-operative complication and early follow-up with 100 TVT-SECUR procedures. J Minim Invasive Gynecol. 2008;15: 480–484.

complication rate low as they had noted an 8% incidence of dyspareunia with 8% reoperation rate secondary to this complication.

In summary, Neuman et al demonstrated that there was no time benefit associated with the TVT-S procedure, there was no efficacy benefit of the TVT-S device, there was a two week TVT-S benefit with regard to lower post-operative pain compared to the TVT-O device (pain that responded to NSAID therapy), and there an 8% TVT-S related incidence (vs 0% for TVT-O) of persistent dyspareunia requiring surgery. When contemplating the efficacy results of this study, one must question the generalizability of these results. The authors reported 87% and 90% complete dryness at three years.

Walsh (2011)[155]

In 2011 Walsh published his systematic review of the literature for articles published between 2006 and December 2010 for 12-month TVT-SECUR outcomes. Walsh excluded studies with less than thirty subjects. It is unclear why the prospective evaluation of Cornu with a mean follow-up of 30 months, and a 40% cure rate, was excluded. Walsh reviewed a total of ten studies. Walsh reported a 76% objective and subjective cure rate at 12 months. Walsh found the "U" approach to be superior "with women twice as likely to be objectively cured compared with the 'H- type' approach (OR 2.2, $P< 0.001$), and with no apparent increase in peri-operative complications". Walsh described a 10% incidence of de novo urge symptoms and noted "based on the present study, rates of *de novo* OAB after a TVT-S procedure do not appear lower, and may indeed be higher, than established MUS techniques".

[155] Walsh, Colin A. "TVT-Secur Mini-sling for Stress Urinary Incontinence: A Review of Outcomes at 12 Months." *BJU International* (2011): 652-57

Although Walsh reported a overall dyspareunia rate of 1%, he noted "absence of data on the number of sexually active women in individual studies precludes an accurate analysis o f this complication. The incidence of dyspareunia after a TVT-Secur mini-sling procedure demands further study". Walsh noted a 2.4% incidence of mesh erosion with the "H" approach and a 0% incidence with the "U" approach. Walsh reported that the herein noted 76% cure rate at 12 months was similar to that of other mid-urethral slings. However, that comment was not supported by the medical literature.

Walsh added "[W]e cannot assume that the use of a mini-sling eliminates the risk of serious adverse outcomes, although the rate of such events after TVT-S procedures remains unknown". Walsh concluded "Until data exist to correctly assess the medium- and long-term cure rates after TVT-S procedures, practitioners must be careful in choosing this surgical approach over more established surgical options". This caution was in line with his cited reference to the 2008 U.K. National Institute for Health and Clinical Excellence guidance document that taught that single incision slings should only be used in the context of research studies or for submission of data to a national registry. This caution from Walsh was also consistent with the caution provide in the systematic review by Abdel-Fattah that same year, "SIMS (single incision slings) should be performed only within a research context".

Tommaselli et al reported on their systematic review of the literature (from January of 2006 to March of 2011) for the TVT-SECUR device.[156] The authors stated that the "Aim of this systematic review was to identify all articles reporting on the efficacy and/or safety of TVT-Secur for the surgical treatment of female urinary stress

[156] Tommaselli GA, Di Carlo C, D'Afierc A, Formisano C, Fabozzi A, Nappi C. Efficacy and safety of TVT-secure in the treatment of female stress urinary incontinence: a systematic review (Abstract number 867). Proceedingsofthe 41stAnnual Meetingofthe International Continence Society (ICS), 2011Aug 29 to Sept 2, Glasgow, Scotland. 2011.

incontinence and to extract data to identify overall cure and success (patients cured plus patients improved) rates, to evaluate TVT-Secur safety and to verify if discrepancies exist between reports from peer-reviewed journals and abstracts presented at international congresses". However, unlike a Cochrane systematic review which is typically limited to RCTs, only thirteen percent of the studies (7) reviewed by Tommaselli were RCTs. Yet there were almost twice as many RCTs (12) available for review.[157] The number of RCTs included by Tommaselli was approximately half the number of the low powered retrospective studies that were included. Less than half of the studies included were published in peer-reviewed journals. At least forty percent of the reviewed studies were limited to abstracts from IUGA/ICS congresses. The studies were not cited. A mean follow-up was not reported. A median follow-up of twelve months was noted.

The authors reported "Overall objective and subjective cure rates were 74.5% and 82.6%, while objective and subjective success rates (cured+improved) were 80.8% and 81.4%". The overall complication rate was reported to be 9.3% and 11.8% when not considering abstracts. The overall de novo urge symptom rate was 7.1% and 9.4% when not considering abstracts". The type of complications included were not described. The authors did report that mesh extrusion (exposure) was the most frequent complication, occurring in 15.2% of cases (15.9% when excluding abstracts). Tommaselli described an overall reoperation rate of 6.4%. The authors noted, "The results of this systematic review seems to indicate that TVT-Secur device objective cure rate does not reach 80%" and concluded, "The data from this analysis seems to suggest that TVT-Secur may have

[157] See RCTs prior to 2011 included in Nambiar A, Cody jD, jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Databaseof Systematic Reviews*2014, Issue 6. Art. No.: CD008709. DOl: 1O.1002/14651858.CD008709.pub2.

lower cure rates in comparison with retropubic and trans-obturator devices, but has limited complication rate".

The authors conclusion with regard to the inferiority of TVT-S efficacy appears to be based on cure not reaching 80%. The range of cures reported for full length retropubic slings from within randomized controlled literature is 80-90%.[158] It is unclear why the authors stated the there was a "limited complication rate". With a median follow-up of 12 months, the limitation of complications can not be assessed. Furthermore, the 16% incidence of mesh erosion is approximately three to ten times higher than that of full-length midurethral slings. It is equally bizarre that Tommaselli's interpretation states that the complication rate was lower than ten percent when their data clearly showed a 15.9% extrusion rate.

Tincello et al. published their prospective 1-year, Ethicon supported, observational study of 1,334 women undergoing TVT-S, TVT, and TVT-O (TVT-WORLD).[159] This manuscript was based on the TVT-World Registry. Objective cure was based on a standing cough stress test. The authors report that "After obturator tension free vaginal tape surgery fewer women had a positive cough stress test than after TVT and SECUR surgery (4 of 110 or 3.6% vs 24 of 187 or 12.8% and 59 of 374 or 15.8%, respectively)". The authors concluded "SECUR appears to have objective and subjective efficacy similar to that of TVT". The editorial review staff at the journal informed Dr. Tincello "*The objective of this study is to examine the effectiveness of a single incision*

[158] Nambiar A, Cody jD, jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Databaseof Systematic Reviews*2014, Issue 6. Art. No.: CD008709. DOl: 1O.1002/14651858.CD008709.pub2.
[159] Tincello, Douglas G., Theunis Botha, Douglas Grier, Peter Jones, Dhinagar Subramanian, Colin Urquhart, Aaron Kirkemo, and Salil Khandwala. "The TVT Worldwide Observational Registry for Long-Term Data: Safety and Efficacy of Suburethral Sling Insertion Approaches for Stress Urinary Incontinence in Women." *The Journal of Urology* 186.6 (2011): 2310-315

sling. For this objective is a registry not appropriate. A RCT should be performed. A registry is especially good for measuring complications". [160]

The reviewer here points out the obvious, a registry, by design, is incapable of demonstrating efficacy. The TVT-World protocol for this registry noted "no hypothesis is being tested".[161] No hypothesis means no p-value. Efficacy is not to be demonstrated. The inappropriate design behind this manuscript was further noted by the U.K. National Health Services (NHS) who rejected the registry stating "If it is intended as a research project, it is suggested that an RCT would be a better way of demonstrating the benefits of TVT SECUR" and "There remains a lack of clarity about the true purpose of this study - ie whether it is an application to set up a registry, or a project-based study to compare 3 different methods of treating stress incontinence, because additional visits and test are, involved as part of research. As submitted, it appears to be neither a true registry nor a true research project". [162]

The authors state that their data demonstrates that the TVT-S is associated with a greater likelihood of a positive I-QOL response than TVT. Unfortunately, the extraordinary bias of this study results in an inability to draw meaningful conclusions. Bias began early by way of a lack of randomization. The sites were forced to perform the first 20 cases as TVT-SECUR. This violates the principles of a registry. Thereafter, the surgeon chose the procedure. This creates a bias at both the level of surgical performance and at interpretation of results. However, the insurmountable bias comes from the extraordinary loss to follow-up.

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[160] ETH.MESH.07094382
[161] ETH.MESH.0718660
[162] ETH.MESH.03878355

Less than fifty percent of the "full analysis set" underwent a test for objective cure, the cough stress test (CST)(671/1398). Taking into account "withdrew" and "death" in the lost to follow-up (missing data) pool, 45% of the TVT-S subjects, 56% of TVT-O subjects, and 60% of TVT subjects were lost to follow-up. While a loss to f/u of less than 5% is ideal, any loss of greater than 20% causes a reader to have a substantial concern about bias.[163] The authors opted to distract the reader from this severe bias. They chose to report failure rates without correction for the loss to follow-up. Although the tabled data includes an asterisk with footer, "Percents exclude missing data", this information is missing from the narrative and not easily spotted. The biased report of an 87 percent objective cure for TVT-S at one year was dramatically different than that reported in prospective trials using the CST.

However, if the authors had accounted for the massive lost to follow-up by utilizing a last observation carried forward method, they would have reported a 47% one-year objective cure rate, a rate closer to that reported in prospective trials described herein. Cornu et al, in their prospective observational evaluation of the TVT-S device, found a 40% cure at a mean of 30 months. North, utilizing a LOCF method, found a 21% cure rate at six months and 10% at two years following MiniTape SIS. If all missing data was considered cured, cure at two years would have been 40%,

The authors indicated that the TVT-S was associated with a quicker return to employment, hobbies, housework and social life. Although this claim is subject to the selection bias noted earlier, it is important to remember that even a valid claim to rapid

[163] Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325: 652-4, Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ : British Medical Journal*. 2006;332(7547):969-971.

recovery would be misleading. The negative impact of failed surgery and re-surgery associated with failed surgery on employment, hobbies, housework and social life, more likely than not, negates any benefit of a possible rapid recovery from TVT-S.

The authors also noted "A major advantage of SECUR appeared to be its potential suitability for an office based procedure rather than surgery requiring for- mal day case hospitalization due to the safety profile". First and foremost, as noted elsewhere, length of stay median times following the TVT-S procedure are often up to 24 hours. Even if modifications in techniques and training resulted in quicker post-op recovery allowing discharge within several hours, office based sling surgery is not realistic in the United States. This is secondary to both a lack of office based reimbursement and state laws prohibiting office-based analgesia. Even if the TVT-S could have been performed in the office setting, this would be a marketing tool and not a health benefit. Futhermore, Ethicon's 2008 poll of surgeons found that the ability to implant a sling in the office was one of the least meaningful sling characteristics to surgeons.[164]

In summary, this Ethicon sponsored manuscript provides no meaningful data and makes misleading claims of TVT-S efficacy.

OTHER COMMENTS

"The TVT Worldwide Observational Registry for Long-Term Data was established in 2007 to provide the real world outcomes of a single incision sling".

[164] ETH.MESH.09951746

- The authors throw Ethicon under the bus regarding initial commercialization: "At that time there were only 2 small published studies showing the 3-month outcome in only 24 patients, including 11 with a U insertion and 13 with a ham- mock insertion". (one was Martan et al with 15 patients. They reported that between one and three months there was a 93% cure rate. This is a foreign language article. The described two cases of folded sling, one resulting in pain, they found one erosion..). All complications were in the 10 pts treated via hammock…that's 20% folding, 10% erosion. One year later, at the annual IUGA scientific meeting, Martan presented their six month data that included a 38% failure rate and 8% incidence of erosion.[165] (one was Delenz et al. This was 16 pts, 6 hammock and 10 U, mean 2 month f/u. Results "all patients expressed satisfaction". This was a foreign language paper. Authors concluded "long follow-up and the incorporation of new patients to the study, will allow to determine the permanence of these good results in the time".[166]

Hinoul et al (2011)[167]

A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence.

[165] Martan A, Masata J and Svabik K: TVT SECURTM System—tension-free support of the urethra in women suffering from stress urinary inconti- nence. Technique and initial experience. Ceska Gynekol 2007; **72**: 42

[166] Sola Dalenz V, Rcci Arriola P and Pardo Schanz J: Stress urinary incontinence surgical correction with third generation sub-mid-urethra sling: TVT- Secur. Actas Urol Esp 2008; **32**: 522.

[167] Hinoul, Piet, Harry A.m. Vervest, Jan Den Boon, Pieter L. Venema, Marielle M. Lakeman, Alfredo L. Milani, and Jan-Paul W.r. Roovers. "A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence." *The Journal of Urology* 185.4 (2011): 1356-362.

In 2011 Piet Hinoul, Ethicon's Worldwide Director of Medical Affairs published, and co-investigators, published their randomized controlled trial comparing the TVT-S device to the TVT-O device. The study excluded women with greater than stage two pelvic organ prolapse and those undergoing any concomitant surgery. All procedures were performed in accordance with Ethicon's instructions for use. The primary outcome was objective cure at twelve months defined as a negative standing cough test (at 300cc or 70% of maximum bladder capacity). A total of 98 and 97 women underwent TVT-O and TVT-S implantation respectively.

The authors noted objective cure, at six months with an equal 11% loss to follow-up between groups, in 65% of the TVT-S subjects and 100% of the TVT-O subjects ($p<0.0001$). Subjective cure was noted in 69% of TVT-S subjects and 95% of TVT_O subjects 9$p<0.01$). At one year, with a dramatic loss in f/u amongst TVT-S and almost no further loss of TVT-O subjects (23% vs. 12%), the authors noted objective cure rates of 84.6% and 97.6% ($p=.002$). Subjective cure rates were reported to be 76% for TVT-S subjects and 92% for TVT-O subjects. It should be noted that loss to follow-up for subjective symptoms at twelve months was 35% for TVT-S and 8% for TVT-O groups. The authors noted no difference in the subjective reporting of urge symptoms between groups.

Subjective reporting of urgency and/or urge incontinence was noted in 23.3% and 23.0% of patients treated with the TVT Secur at 6 months and 1 year vs 16.3% and 16.7% with the TVT-O, respectively. These differences did not attain statistical significance.

The authors noted a 7.3% erosions rate amongst TVT-S subjects and a 1% incidence amongst TVT-O subjects with the odds of erosion after TVT-S being 7.6 compared to TVT-O. It should be noted that one TVT-S erosion was noted at 12 months. At this point there had already been a 35% loss to f/u. It is very important to realize that the authors included all of those patients lost to f/u as non-erosions. One needs to review the figures to realize this. If the authors would have done one of applied one of the more typical methods for managing missing data, the TVT-S erosion rate would have been reported as either 9% or 29% (excluded the missing data from the numerator and the denominator or intent to treat with the missing data added to both the numerator and the denominator). Of additional note, all of the TVT-S erosions required surgical intervention (7% re-operation rate for erosion). None of the TVT-O subjects required resurgery for erosion. The authors further identified higher risk of re-operation for SUI amongst the TVT-S group (OR of 2.3, CI 1.9-2.7).

The total number of TVT-Subjects re-operated on for SUI or scheduled for re-operation at time of one year follow-up was 14 (15%). Combining resurgery for mesh erosion and resurgery for recurrent or persistent SUI, 22% of TVT-S subjects required re-surgery within twelve months of TVT-S implantation. With at 35% loss to follow-up, the actual number of re-surgeries may have been much higher. Additional findings included a mean decrease in operative time of two minutes with TVT-S (sig), significantly higher blood loss with TVT-S, and significantly longer catheterization with TVT-S,

Hinoul et al noted, “In 1 study patients appeared to prefer a minor procedure with a lower risk of complications and would accept a lower success rate under those

circumstances".[168] Hinoul et al are herein misrepresenting the findings of a 2002 ICS abstract (or are representing the conclusion thereof without examining the data). This abstract described the poling of one hundred women undergoing urodynamic testing with regard to expectations of treatment, acceptability of symptoms, and acceptability of treatments. However, this statement is not supported by the findings of Robinson et al. The study did asked women two separate questions: Would they accept a Major surgery with an 85% success rate and a 2% risk of self catheterization and would they accept a Major surgery with an 85% success rate and a 2% risk of self catheterization. Fifty-seven percent indicated that they would not accept the major surgery and forty-three percent indicated they would not accept the minor surgery. Hence, the results simply indicated that women preferred a smaller surgery.

There were no questions that combined decreasing efficacy and decreasing complications. Even if these investigators had asked these questions and had found that women would accept 85% efficacy rather than higher efficacy for a complication rate that was reduced to 2%, this would not apply to the TVT-S procedure, a procedure know to be with a lower efficacy and higher complication rate. However, the UDI questionnaire scores for stress and urge incontinence were significantly higher (worse) amongst the TVT-S subjects ($p<0.01$). The authors did find a significant difference in post-operative pain scores that disappeared after the first two weeks ($p<.01$). However, after day five, there was no significant difference in postoperative analgesic use. Although ADLs were significantly less effected in the first week amongst TVT-S subjects, not significant difference was noted thereafter.

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[168] Robinson D, Anders K, Cardozo L et al: What womenwant their interpretation of concept of cure. Neurourol Urodyn 2002; 21: 429.

The authors concluded that the objective cure rate for SUI favored TVT-O over TVT Secur. The authors also concluded "The study failed to confirm the anticipated lower perioperative morbidity rate of TVT Secur since we noted increased blood loss, higher tape exposure and bladder injury rates, and a more common need for surgical re-intervention. Considering possible economic benefits or patient preferences ,the role of TVT Secur remains to be studied". It is important to realize that five years after the introduction of TVT-S, Ethicon's medical director still remains unsure of the role of TVT Secur. As noted herein, he is making an erroneous reference to the patient preferences cited in the Robinson study. Futhermore, he is contemplating the economic benefit associated with less discomfort with walking in the initial two weeks, an economic benefit, if real, that would be completely negated by the major economic harm created by persistent incontinence, recurrent incontinence, and the 22% re-surgery rate noted by Hinoul et al.

In summary, Ethicon's Worldwide Director of Medical affairs has found that the TVT-S offers inferior efficacy to the TVT-O device and provides not meaningful benefit. Dr. Hinoul and co-investigators have also demonstrated that the TVT-S device is associated with a significantly higher rate of erosion and resurgery compared to the TVT-O device. Finally, Hinoul et al notes that, five year since its release to the market, the TVT-S device has not clear role in the treatment of incontinence. Additionally, any efficacy therein noted, could not be generalized as Hinoul excluded patients with greater than stage two prolapse or undergoing concomitant surgery.

2012

In 2012 Hota et al published their findings, TVT-SECUR (Hammock) Versus TVT-Obturator: a Randomized Trial of Suburethral Sling Operative Procedures (Ethicon Sponsored).[169] This was a single center, non-blinded, randomized trial. Primary outcomes were SUI on cough stress test (300 CC) and quality of life and symptoms. Seventy-seven women were randomized. Assessments were made a three months and one year. The failure rates of TVT-S and TVT-O were 55% and 9% respectively. The authors determined that the risk of a positive post surgical cough stress test was six times higher with TVT-S. There were not significant differences in quality of life. Secondary to investigator concerns of a high incidence of postoperative positive CSTs in women who had undergone the TVT-S procedure, the study was terminated early and an analysis was performed.

- At one year, mesh extrusion was noted in 19% of the TVT-S group and 0% of the TVT-O group (p=0.002)
- Resurgery for persistent or recurrent SUI confirmed by UDT and positive CST was performed in 19% of the TVT-S group and 0% of the TVT-O group (P=0.002).
- The failure rates of TVT-S and TVT-O were 55% and 9% respectively
- TVT-S and TVT-O procedures result in similar improvements in quality of life and symptoms. However, the QOL questionnaires included POP and bowel symptoms, and the authors noted that questionnaires "were not specific to urinary

[169] Hota, Lekha S., Katherine Hanaway, Michele R. Hacker, Anthony Disciullo, Eman Elkadry, Patricia Dramitinos, Alexander Shapiro, Tanaz Ferzandi, and Peter L. Rosenblatt. "TVT-Secur (Hammock) Versus TVT-Obturator." *Female Pelvic Medicine & Reconstructive Surgery* 18.1 (2012): 39-43.

symptoms alone" and hence patients may have hence been "satisfied with an improvement in their symptoms despite a positive CST result.

The authors postulated regarding high failure rate and high complication rate

- "During the introducer removal process. the original tensioning may have been compromised, as the introducer was moved back and forth in an attempt to release the sling from the introducer"
- "There also was an increased incidence of mesh exposure in the *TVT-S* group. Although the etiology of this complication is unclear, we theorize that the sharper edges of the TVT-S introducer potentially create more trauma to the vaginal epithelium and may result in higher erosion rates".

Single-Incision Mini-Sling Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence.[170]

In 2012 Barber et al published the results of their RCT comparing TVT-SECUR "U" method to TVT retropubic. They noted that Lee et al had found quality of life scores favored the TVT-SECUR "U" method over the "H" method. To reduce possible patient bias and ascertainment bias, both the individual and research staff performing postoperative evaluations were blinded to treatment assignment throughout the course of the study by means of sham suprapubic incisions created in the TVT-S group. This was a non-inferiority trial. The primary purpose of this trial was "to test the hypothesis that the TVT-S is not inferior to the TVT in this patient population" at one year. The TVT-S failed to meet the non-inferiority criteria.

[170] Barber, Matthew D., Alison C. Weidner, Andrew I. Sokol, Cindy L. Amundsen, J. Eric Jelovsek, Mickey M. Karram, Mark Ellerkmann, Charles R. Rardin, Cheryl B. Iglesia, and Marc Toglia. "Single-Incision Mini-Sling Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence." *Obstetrics & Gynecology* 119.2, Part 1 (2012): 328-37.

One year after surgery, the cure rate was noted to be similar between groups. However, incontinence severity at one year was significantly greater with TVT-Secur, with 16% of TVT-SECUR patients having severe incontinence compared to 5% of the TVT-retropubic patients. Although the authors concluded that “the mini-sling (TVT-SECUR) placed in the "U" position results in similar subjective cure rates to TVT 1 year after surgery but postoperative incontinence severity is greater with the mini-sling than with TVT, only the later is a correct conclusion.

Unfortunately, the data was subject to selection bias. The authors elected to exclude patients with mixed incontinence (urodynamic evidence of detrusor overactivity). Previous investigators such as Mechia et had shown that this population of patients have lower cure rates following TVT-S. Hence, any results of this study could not be generalized to the patients with stress incontinence but would apply only to those with pure stress incontinence (and not urge incontinenc). Additionally, the investigators chose to deviate from the labeled instructions for both the TVT and TVT-S procedures, performing methods that may have favored higher efficacy in the TVT-S group and lower efficacy in the TVT group. The investigators chose to perform the TVT-S procedure with the modification of Neuman, a modification Neuman believed to increase efficacy by 12%. Whereas the TVT retropubic IFU taught “To avoid putting tension on the tape, a blunt instrument (scissors or forceps) should be placed between the urethra and the tape during removal o f the plastic sheaths”, Barber et al taught that a spacer should be placed between the sling and the urethra. Although they do not describe the spacer, they suggest that a spacer should be able to slip under the sling post placement. Hence, the results of this study can not be generalized to patients undergoing standard

TVT-S and TVT retropubic procedures. The results of this study can only be considered amongst patients with pure SUI undergoing the Neuman modification of the TVT-SECUR procedure.

Approximately 5% of the women in the TVT-Secur group were implanted with a second device. The effect of using a second device is not known, confounds the data and skews the results. It is more likely than not that this ad-lib surgery biased toward an increased TVT-S efficacy. These subjects should have been treated as missing data. According to the protocol, missing was to be considered failures for the primary analysis. If this was adhered to, the mini sling subjective cure rate would have been reduced from 56% (72/129) to 52% (67/129). This may have resulted in a p value less than 0.05. Additionally, whereas all of the TVT-retropubic subjects had the assigned intervention, approximately 9% of the TVT-S group did not. This was resultant to "technical difficulties or a device malfunction of the mini-sling at initial implantation that resulted in placement of TVT (n=6) or other retropubic mid-urethral sling (n=1) or use of a second mini-sling device (n=5) at the index surgery. All twelve of these subjects should have been treated as missing data for the intent to treat analysis. Curiously, the authors intent to treat subjective cure analysis added five cures rather than subtracting twelve. This last observation carried forward–intent to treat analysis, consistent with the protocol, would have reduced the intent to treat subjective cure rate from 57% (77/136) to 44% ((72-12)/136). This may have resulted in a p value less than 0.05. The analysis of the secondary outcomes was also tainted by the failure to treat as missing data the seven women of the TVT-SECUR group who were treated with standard MUS (and the 5 women who underwent implantation with a second TVT-S device).

The authors of this study reported "The minisling group was more likely to be discharged without a catheter than those in the TVT group". However, this is a misleading statement. The results of this study were also confounded by hysterectomy. Significantly more women in the TVT retropubic group underwent concomitant hysterectomy. Hence, it is likely that this effect was attributable to the hysterectomy. The authors also noted that there was no significant difference in duration of catheter use. This suggests that the difference may have been simply secondary to a slightly earlier discharge of the patients in the TVT-retropubic group. Although not statistically significant difference in length of hospital stay was noted, the increased number of hysterectomies in the TVT-retropubic group also confounds this. The authors reported significantly lower pain scores prior to but not after day number four. This finding is similarly confounded by the significantly greater number of hysterectomies performed in the TVT-retropubic group.

The authors also provided a misleading report of 81% complete resolution of SUI following the TVT-S procedure. Although the authors' definition of "complete resolution" is not defined, it appears that this is a subjective measure based on the Patient Global Impression of Improvement. The authors appear to have categorized both "very much better" and "much better" responses as "complete resolution". As "complete" means total, the authors' report of 81% complete resolution of SUI misleads the reader to believe that 81% were 100% better. Even if one was to somehow understand that "complete resolution" meant "much better", it would not be obvious that the 20% of the patients did not respond to the questionnaire. Using an intent to treat analysis and a last observation carried forward, 63% of the TVT-S subjects and 71% of the TVT-retropubic

subjects would have met the authors' definition of "complete resolution". Interesting, the 63% TVT-S "complete resolution" number is very close to the 57% that reported themselves to be "dry" at 12 months.

In summary, this study failed to meet its primary objective, to demonstrate non-inferiority of the TVT-SECUR device ("U" method). The study found that incontinence severity was significantly greater one year after a TVT-Secur than after a TVT-retropubic sling. As noted herein, these authors excluded patients with mixed urinary incontinence and deviated from the TVT-S IFU. Hence, the limited findings cannot be generalized to all women undergoing TVT-S implantation and can not be applied to any TVT-S implanted in accordance with the teachings of the Ethicon IFU. Secondary to the questionable handling of the missing data (described above), the findings as described by the authors, more likely than not, dramatically overestimate the efficacy and underestimate the adverse events associated with TVT-S. Lastly, the finding with regard to pain and catheter use are confounded and likely erroneous.

The authors concluded, "The minor improvements in complication rates and the postoperative patient experience demonstrated by TVT SECUR seem to be overshadowed by a significantly greater incontinence severity after surgery, however. This highlights the need for rigorous clinical trials evaluating the efficacy and safety of new innovations in treatment for SUI relative to standard retropubic or transobturator mid-urethral slings before widespread adoption".

Cornu et al (2012)[171]

In 2012 Cornu et al reported on their five-year prospective observational study of 45 consecutive women undergoing implantation with the TVT-S device.[172] Mean follow-up was 59 months. This was a follow-up analysis of their midterm evaluation reported in 2010 (30.2 month mean follow-up). Cure was defined as "no stress-related leakage, using no pads, and satisfied with the treatment (PGI-I score: 1 or 2)". Since the midterm analysis with a 30 month mean follow-up, the cure rate had decreased from 40% to 31%. There was a slight increase in the percentage of women whom went on to repeat incontinence surgery. This number increased to 29%. The authors concluded, "In our experience, the TVT SECUR device definitely did not stand the test of time, with a 31% success rate after 4.5-yr of follow-up, and it should not be considered a valuable option for SUI management unless supplementary data are provided regarding its long-term outcome." One of the authors was a paid consultant of Ethicon.

2013

Tommaselli et al 2013[173]

In 2013 Tommaselli et al published the results of their randomized controlled trial comparing the TVT-SECUR ("H Method") to the TVT-O device.[174] The primary endpoint was objective cure rate at 36 months by a negative the challenge stress test. "The primary endpoint was evaluated with a noninferiority study design". The TVT-O

[171] Cornu, Jean-Nicolas, DaphnÃ© LizÃ©e, Philippe SÃ¨be, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, and FranÃ§ois Haab. "TVT SECUR Single-Incision Sling After 5 Years of Follow-Up: The Promises Made and the Promises Broken." *European Urology* 62.4 (2012): 737-38.
[172] Cornu, Jean-Nicolas, DaphnÃ© LizÃ©e, Philippe SÃ¨be, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, and FranÃ§ois Haab. "TVT SECUR Single-Incision Sling After 5 Years of Follow-Up: The Promises Made and the Promises Broken." *European Urology* 62.4 (2012): 737-38.
[173] Tommaselli, Giovanni A., Alessandro Dâ□™Afiero, Costantino Di Carlo, Carmen Formisano, Annamaria Fabozzi, and Carmine Nappi. "Tension-Free Vaginal Tape-O and -Secur for the Treatment of Stress Urinary Incontinence: A Thirty-SixMonth Follow-Up Single-Blind, Double-Arm, Randomized Study." *Journal of Minimally Invasive Gynecology* 20.2 (2013): 198-204
[174] Tommaselli, Giovanni A., Alessandro Dâ□™Afiero, Costantino Di Carlo, Carmen Formisano, Annamaria Fabozzi, and Carmine Nappi. "Tension-Free Vaginal Tape-O and -Secur for the Treatment of Stress Urinary Incontinence: A Thirty-SixMonth Follow-Up Single-Blind, Double-Arm, Randomized Study." *Journal of Minimally Invasive Gynecology* 20.2 (2013): 198-204

was implanted in a manor consistent with the TVT-O IFU. The TVT-S device was not implanted with modified method of Neuman. Patients with greater than stage two pelvic organ prolapse were excluded. A single surgeon who had already performed more than forty of each procedure performed all surgeries at each of the two sites. It should be noted that one of these two surgeons had most likely performed over one hundred TVT-Secur procedures prior to this study.

Dr. Tommaselli reported that he had performed over fifty TVT-SECUR procedures over one year prior to the start of this study.[175]One of these two surgeons was a paid consultant of the manufacturer (Dr. Afiero). At total of 77 women were implanted with the TVT-O device and 75 women were implanted with the TVT-S device. Two women in the TVT-S group (2/77 or 2.6%) were moved to TVT-O implantation secondary to technical difficulties in the TVT-S procedure encountered by the experienced surgeon.

Tommaselli et al reported no differences in 36 month objective and subjective cure rates for TVT-O and TVT-S groups (86% vs. 78% and 80% vs. 75%). Loss to follow-up was 14% in the TVT-O group and 18% in the TVT-S group. Using a LOCF analysis of missing data, the authors reported TVT-O and TVT-S objective cure rates of 78% and 68%. Although the authors report that there was no significant decline in cure rates over the follow-up period in both groups, the data is not disclosed. The authors reported that the TVT-S procedure was approximately three minutes quicker ($p<.05$), and time to first void was approximately 28 minutes quicker in the TVT-S group. Although the authors noted post-operative pain was significantly higher in the TVT-O group, this

[175] Tommaselli, G., Costantino, D. C., Gargano, V., Formisano, C., Scala, M., Nappi, C., Efficacy and safety of TVT-O and TVT-Secur in the treatment of female stress urinary incontinence: 1-year follow-up. Int Urogynecol J (2010) 21:1211–1217. Prior to March of 2007, Dr. GT had peformed greater than 50 TVT-S procedures.

effect was not associated with increased analgesic use and did not demonstrated beyond 24 hours. The authors noted that moderate and severe bleeding was more common in the TVT-S group. Severe bleeding in a TVT-S patient resulted in a blood transfusion and a three day hospital admission. One patient, a TVT-S patient, had complete urinary retention that necessitated a repeat surgery with tape incision. Although not statistically significant, the rate of de novo urgency was twice as high amongst women in the TVT-S group. There were no differences noted in quality of life scores.

The authors concluded, "TVT-Secur seems to be noninferior to TVT-O, causes less postoperative pain, and has a low complication rate". It is unclear what "seems means. This is an ambiguous term. Either the study met or did not meet non inferiority criteria. A 2.6% procedural abandonment rate is not low. As noted elsewhere in this monograph, it is unlikely that the short term difference in pain is of clinical significance as it was not associated with any significant difference in analgesic use.

The results of this study cannot be generalized to women with SUI being implanted in the community with TVT-S. The results of this study are specific to specialist pelvic surgeons who have performed more than forty TVT-S procedures, who are operating on women with less than stage three prolapse, who are implanting the TVT-S according to the method of Neuman (a method not described in the TVT-S IFU).

It should be noted that, in 2010, Dr. Tommaselli published his observational study of TVT-S vs TVT-O. Tommasselli et al noted that "in order to obtain the statistical power necessary to evaluate if TVT-Secur is as effective as TVT-O, considering as clinically relevant a difference of 5%, at least 350 patients per arm would be needed".

This is approximately ten times the number evaluated herein. This study performed herein included only approximately one fifth of this number.

2014

Schimpf et al published their systematic review of the literature.[176] These authors reviewed fifteen randomized controlled studies comparing TVT-S to other midurethral slings (MUS). Six studies were available for assessment of objective cure. All compared TVT-O to TVT-S (all but one used Hammock). The authors found TVT-S to be inferior to TVT-O. The odds ratio was 4.16 (CI 2.15-8.05). Five studies were available for assessment of subjective cure. Two studies compared TVT to TVT-S (one H and one U). Three studies compared TVT-O to TVT-S (2 H and one U). Subjective cure was significantly more likely with full length MUS with an odds ration of 2.65 (CI 1.36-5.17). Not a single study found either a higher objective or subjective cure rate associated with the TVT-S procedure. There was insufficient data to assess patient satisfaction. The authors concluded that dyspareunia and urethral perforation were more likely with the minisling.

Although the authors reported equivalent erosion risk amongst all MUS types, it does not appear as though a statistical analysis was performed. The authors indicated that there was no significant difference in rates of OAB. However, the analysis was not provided. The authors indicated that the minisling was associated with a lower risk of groin pain. However this was misleading, as their tables showed equivalence to retropubic slings. The authors concluded, "Traditional MUS are significantly superior to minislings for cure outcomes" and "Dyspareunia is more common with minisling than

[176] **Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211:71.e1-27.**

either retropubic or obturator sling, but absolute rates are low for all types of slings".

The schimpf publication is flawed in various other ways as well. For example, it does not appear to take into consideration patients who dropped out and were not evaluated, thereby inflating the denominator skewing the results. Other mistakes were made elsewhere throughout the study, calling into question any conclusions drawn therefrom.

Nambiar et al (The Cochrane Group) published their systematic review of the literature, Single incision sling operations for urinary incontinence in women (Review) .[177] The authors identified 31 randomized or quasi-randomized controlled trials in which a single incision sling was compared to a full length midurethral sling. Eighty percent of the data came from studies that utilized TVT-SECUR as the single incision sling. No data on single incision slings (SIS) vs retropubic MUS was available. The authors found that "Women were more likely to remain incontinent after surgery with single-incision slings than with retropubic slings such as tension-free vaginal tape *(TVT)* (121/292, 41% vs 72/281, 26%; risk ratio (RR) 2.08, 95% confidence interval (CI) 1.04 to 4.14)".

The authors also found that the rate of incontinence following a single incision sling (SIS) was almost three times the rate of incontinence following a TVT-O sling. The risk of objective failure was four fold higher with single incision slings. Compared to bottom-up retropubic slings, the authors found the single incision sling to be associated with double the risk of post implant stress incontinence (statistically significant). Compared to "in to out" obturator midurethral slings as well as all obturator slings (as a group), the authors found the single incision sling to be associated with double the risk of post implant stress incontinence (statistically significant). Compared to "in to out"

[177] Nambiar A, Cody jD, jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Databaseof Systematic Reviews*2014, Issue 6. Art. No.: CD008709. DOl: 1O.1002/14651858.CD008709.pub2.

obturator midurethral slings the authors found the TVT-S device to be associated almost five times the risk of no improvement The authors noted that this effect was principally due to the TVT-S device. Repeat surgery for SUI was six times more likely with a single incision sling (3 times more likely than all obturator slings). The authors noted that the TVT-SECUR device drove this finding. Once the TVT-S data was removed, the rate of resurgery was no longer statistically significant. In their final discussion, the authors reported, "TVT-Secur is the single-incision sling that has been studied most widely, and the evidence clearly shows it to be inferior to both retropubic slings and inside-out transobturator slings in achieving cure of stress incontinence while leading to higher risk of adverse events. It does not have a fixation system, and this may have contributed to its poor performance". The authors concluded, "TVT-SECUR is inferior to TVT and has already been withdrawn from clinical use".

Nambiar et al also found a significantly higher incidence of adverse events associated with the single incision sling. The relative risk of erosion was almost 4 times that of other midurethral slings. The relative risk of erosion was almost 4 times that of other midurethral slings.[178] The incidence of mesh exposure with TVT-S was found to be 6% compared 1% with TVT-O. The relative risk of erosion into the urethra or bladder was almost 18 times that of other midurethral slings, and mean blood loss was significantly higher with single incision slings.[179] These are the same adverse events that the developers of single incision slings proposed would be reduced. The authors found that the relative risk of de novo urgency following a single incision sling was 2.39 (CI

[178] The adverse event profile was significantly worse,specifically consisting of higher risks of vaginal mesh exposure(RR 3.75,95% CI 1.42 to 9.86), bladder/urethral erosion (RR 17.79, 95% CI 1.06 to 298.88) and operative blood loss (mean difference 18.79, 95% CI 3.70 to 33.88).

[179] The adverse event profile was significantly worse,specifically consisting of higher risks of vaginal mesh exposure(RR 3.75,95% CI 1.42 to 9.86), bladder/urethral erosion (RR 17.79, 95% CI 1.06 to 298.88) and operative blood loss (mean difference 18.79, 95% CI 3.70 to 33.88).

1.25 to 4.56) compared to other midurethral slings. Compared to bottom-up retropubic slings, the TVT-SECUR was associated with more than two times the risk of de novo urgency. Compared to "in to out" obturator midurethral slings as well as all obturator slings (as a group), the authors found that repeat surgery for SUI was six times more likely with a single incision sling (3 times more likely than all obturator slings.

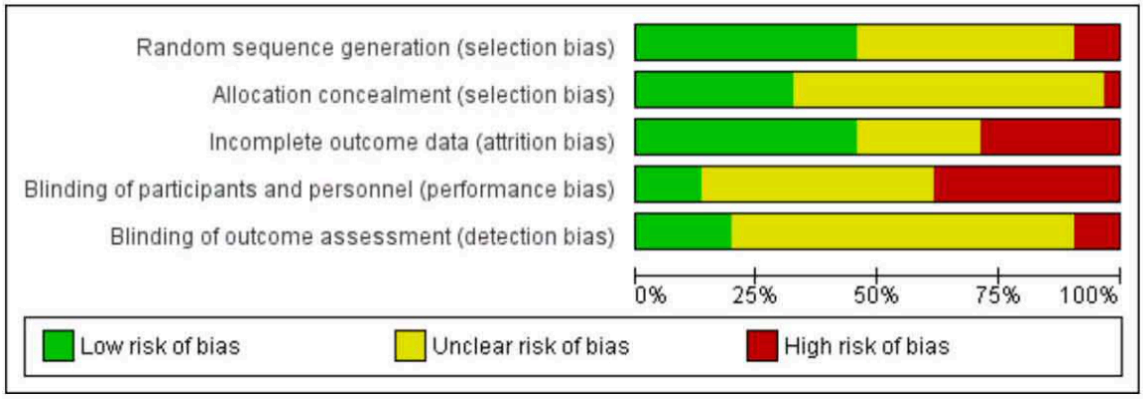
Additionally, Nambiar et al found that the TVT-S device was associated with a 2.5 fold increased risk of additional surgery for complications (statistically significant). Nambiar et al also found that quality of life was significantly better after the bottom-up retropubic sling compared to SIS. Four of the five trials evaluated were TVT-SECUR trials. Compared to "in to out" obturator slings, no quality of life difference was noted.

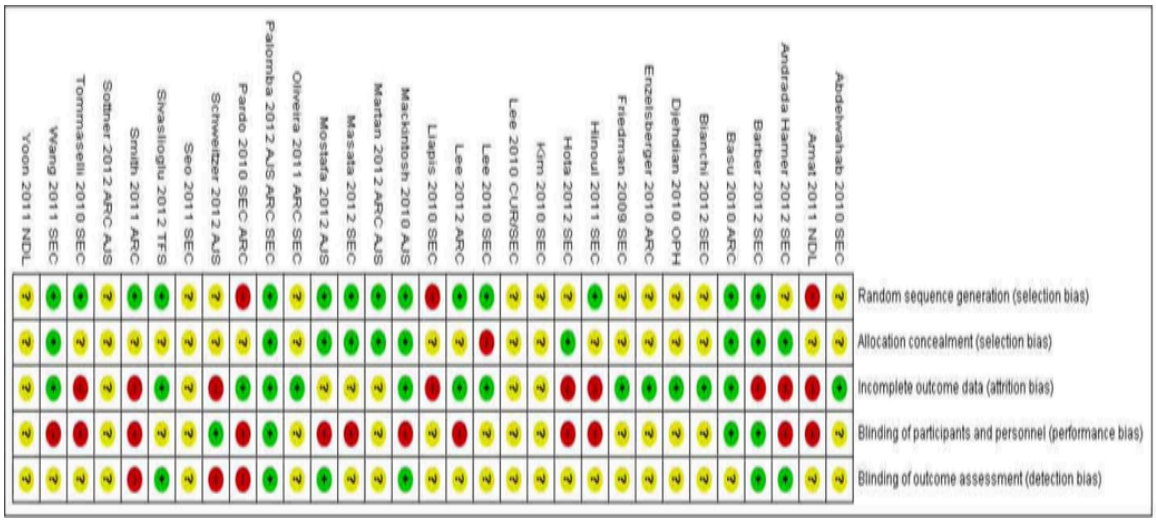
The authors found no significant difference in retentive symptoms. Compared to obturator slings, the authors were able to identify a one-minute time savings associated with single incisions slings. Although this reached statistical significance, the authors reported, "the clinical and economic advantages of a one- minute reduction in theatre time are likely to be negligible". Although the relative risk of postoperative pain with single incision slings was found to be 0.29 and the rate of long-term pain and discomfort was "marginally lower", the authors reported "the clinical significance of these differences is questionable". The authors added that Risks of postoperative and long-term groin/thigh pain were slightly lower with single-incision slings, but overall evidence was insufficient to suggest a significant difference in the adverse event profile for single-incision slings compared with transobturator slings".

The reported a high degree of bias amongst the qualifying studies. This is demonstrated in two figures copied and included herein (FIGURES). The Cochrane group noted that full blinding was only performed in a single study. This was don via sham incisions (Barber 2012). Unfortunately, that same study was considered to have a high risk of bias secondary to a high loss to follow-up. Nine of the thirty-one studies were considered to have a high risk of bias secondary to attrition bias.

Nambiar et al commented on four other systematic reviews. They noted that Abdel-Fattah (2011), limited to six RCTs, found "that single-incision slings were associated with inferior patient-reported and objective cure rates on short-term fellow-up, as well as higher reoperation rates for SUI, while having a significantly shorter operative time, lower day one pain scores and less postoperative groin pain". They noted that Jeffery (2011) only included three RCTS and "Overall cure rates were reported to range between 70% and 81%, with less than 1% risk of bladder injury and groin or hip pain". They noted that Tommaselli (2011), was of similar design to Jeffery, included only seven RCTs and concluded that the objective cure rate for TVT-Secur did not reach 80% (significantly lower than that of standard mid-urethral slings). Nambiar reported "Overall the results of these reviews are in keeping with ours, bearing in mind the lower number of randomized studies included in the above reviews. The conclusion of poor performance of TVT-Secur has been reiterated in this review, which only strengthens this conclusion". In their final discussion, the authors stated, "TVT-Secur is the single-incision sling that has been studied most widely, and the evidence clearly shows it to be inferior to both retropubic slings and inside-out transobturator slings in achieving cure of stress incontinence while leading to higher risk of adverse events. It does not have a fixation

system, and this may have contributed to its poor performance".In their final conclusion narrative, Nambiar et al reported, "TVT-SECUR is inferior to TVT and has already been withdrawn from clinical use".





In October of 2014 Coskun et al reported their prospective evaluation on the treatment single incision sling complications.[180] The complications for which sling excisions were performed included pelvic pain (65%), Dyspareunia (59%), and

[180] Coskun, Burhan, Rebecca S. Lavelle, Feras Alhalabi, Gary E. Lemack, and Philippe E. Zimmern. "Mini-slings Can Cause Complications." *International Urogynecology Journal*26.4 (2014): 557-62.

obstructive urinary symptoms (30%). Seventy-six percent had more than one complaint. Only 35% were cured following surgical excision. The authors reported that attempts were made to remove the majority of the device or the entire device. The success rate of such attempts is not noted. The authors noted that, amongst those women with no history of prior mesh placement, sling removal did not resolve the dyspareunia (100% failure to respond to surgery). Sling excision did not resolve pelvic pain in 42% of women who had on a single incision sling (no other mesh). Twenty percent of those with obstructive symptoms failed to improve following sling excision. The overall success rate, cure rate, of sling excision was 35%. The authors also reported their experience with minisling demonstrated only 20% of patients to be continent following such. Seconary to the low efficacy of surgical treatments of complications, the authors concluded, "Therefore, caution is required and patient counseling is important".

2016

National Institute for Health and Clinical Excellence (NICE)

Interventional procedure guidance 262 (2016)[181]

NICE is the independent organization responsible for providing evidence-based guidance on health and social care. In 2005 NICE merging with the Health Development Agency of the United Kingdom. NICE creates guidelines with evidence-based recommendations on a wide range of topics in health, public health and social care. The nice charter includes the following narrative. A description of NICE and its responsibilities is found in the previously described 2008 NICE guidance for single incision slings. In October of 2016, NICE published its update to its 2008 guidance for

[181] National Institute for Health and Clinical Excellence. Interventional procedure guidance 566. Single-incision short sling mesh insertion for stress urinary incontinence in women. October 2016. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG566

single incision slings, Single-incision short sling mesh insertion for stress urinary incontinence in women.[182]

The introduction to the guidance included,"Your responsibility": "This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer".

The updated nice recommendations included:

> Clinicians wishing to do single-incision short sling mesh insertion for stress urinary incontinence in women should:
>
> > Inform the clinical governance leads in their NHS trusts.
> >
> > Ensure that patients understand the uncertainty about the procedure's safety and efficacy, including that there is the potential for the procedure to fail and for serious long-term complications from the device, and that the mesh implant is intended to be permanent so removal, if needed, may be difficult or impossible.
> >
> > Provide patients with clear written information. In addition, the use of NICE's information for the public is recommended. Audit and review clinical outcomes of all patients having single-incision short sling mesh insertion for stress urinary incontinence in women.
> >
> > Patient selection should be done by a multidisciplinary team with experience in the assessment and management of women with stress urinary incontinence.

[182] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 566. Single-incision short sling mesh insertion for stress urinary incontinence in women. October 2016. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG566

> This procedure should only be done by clinicians with specific training in transobturator surgical techniques.
>
> Removal of a short sling mesh should only be done by people with expertise in this specialized surgery.

The authors of this guidance document described their meta-analysis of the literature and the existing data on single incision slings. The authors noted that in the 2014 Cochrane systematic review found a significant decrease in efficacy of single incision slings compared to other mid-urethral slings. The authors noted that that this systematic review found patients more likely to remain incontinent following the a single incision sling. They pointed out that the this difference in efficacy could not be determined once the TVT-S data was excluded and that the Cochrane group found that the high risk of incontinence found with single incision slings was mainly associated with the use of the TVT-SECUR device.

The NICE group noted that, in their meta-analysis that excluded TVT-S, no difference in efficacy (compared to other mid-urethral slings) was noted. The NICE group noted that the Cochrane meta-analysis found the mesh erosion was significantly higher with single incision slings. However, this risk was not identified in its (NICE) meta-analysis that excluded the TVT-S data. They further noted that they found a significant decrease in post-operative pain once they excluded the TVT-Secur data. They found de novo OAB symptoms to be significantly higher at five years amongst SIS patients. Repeate continence surgery rates were not statistically significantly different once the TVT-SECUR trials were excluded.

EFFICACY SUMMARY

By the end of 2006, the year of product launch, Ethicon was aware that the efficacy of its TVT-SECUR product was inadequate. Ethicon's internal document, "Concerns from J&J Australia in regards to anecdotal reports of high post procedure incontinence ~6wks post op TVT-SECUR", noted *"In comparison since launch in Aug 2006, TVT- SECUR does have significantly higher complaint rate then pre-existing products".* This internal document noted that higher rates of post-procedural incontinence in Germany had lead to a formal Corrective Action Preventative Action (CAPA) report, that determined the root cause to be preceptor training.[183] Within this same internal document Ethicon provided tabulated results comparing the effivcacy of its TVT-SECUR "U" and TVT-SECUR "Hammock" method. The U and Hammock six-month objective cure rates by CST were reported to be 71% and 57% respectively with an overall 64% cure rate. This was substantially lower than cure rates reported for its TVT and TVT-O devices. This document, a PowerPoint presentation, also provides that Ethicon is following 233 women in a "safety set" that has demonstrated 94% success. Although no description of this set is provided, there was a 40% loss to follow-up, making the data biased and unreliable. Ethicon attributed the high failure and complaint rate to be a result of defective training. Following re-training of the surgeons, Ethicon noted that the Australian surgeons continued to report greater than a 50% failure rate.

On June 18th of 2008, a meeting between Ethicon engineer and co-inventor of the TVT-S device, Dan Smith, Ethicon key opinion leader and consultant, Carl Nilsson , and other Ethicon representatives was transcribed.[184] The topic was Project Scion. This

[183] TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770
[184] **ETH.MESH.04048515**

project appeared to focus on the development and deployment of an improved version of the TVT-S device.

Dr. Nilsson noted that there was a "Huge complication rate with TVT-S in Germany because of training concerns" and "There is no documentation that Mini-Sling is safer and with equal efficacy as TVT". He added:

- That the Hammock had much lower efficacy than the "U" method and "mini-sling hammock will never work"
- He questioned, "Will there ever be an exitless mini-sling that will work?"

Dan Smith stated that Ethicon would like DR. Nilsson to be involved in the development of the improved device. Dr. Nilsson indicated that a minimum of 1 year data would be needed prior to launch. Ethicon's Jason Hernandez noted that during a pre-clinical trial, all iterative changes would require an FDA IDE.

Less than one week following this email exchange Ethicon's Worldwide Group Marketing Director, Harel Gadot, emailed a presentation entitled "Next generation sling. Evaluating opportunities, considering risks" to numerous Ethicon employees including its World Wide Medical Director and Director of Research and Development.[185] The presentation asked the following question*, "What will be our value proposition should MiniArc (or any other exit less sling) get the same efficacy as TVT O/TVT?"* Ethicon herein demonstrates its awareness and concern of the fact that its TVT-SECUR device has inferior efficacy. Furthermore, Ethicon herein demonstrates that it has considered the possibility that the failure of its TVT-SECUR device is at least in part secondary to the experimental, non-barbed, Ethisorb ends and experimental introducer system (The AMS

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[185] ETH.MESH.09951746

MiniArc utilized a conventional barbed anchor and placement needle). This same marketing presentation indicated that in year three (2008), a year typically associated with a robust increase in sales of a new device sales were TVT-SECUR sales were down 25% in the U.S. and 37% in EMEA whilst the rest of the TVT family of devices remained with steady or growing sales.

In 2007 manuscripts published in peer reviewed medical journals demonstrated cure rates as low as 64% and suggested a substantially lower efficacy of the Hammock method compared to the "U" method. Investigators noted that TVT-SECUR should not be considered a first choice in the treatment of SUI and that it was unclear if the novel procedure would have future in the treatment of SUI. Ethicon was aware of this and continued to sell its TVT SECUR device without such warnings. In 2008 efficacy reports were even more concerning with reports as low as 31% at one year and a report of efficacy being half that of the standard TVT at three years. By 2009 reports of efficacy of the mini-sling became even more concerning, with North et al reporting a cure rate as low as 10% at two years. By 2010 there was even more validation of the above noted excessive failure rate and the dramatic increase of such rate over time.

Cornu et al noted a 33% recurrent incontinence rate at a mean of 30 months. By 2011 multiple systematic reviews had validated the low efficacy of the TVT-SECUR device. The inferiority of the "Hammock" method, compared to the "U" method was also validated. In 2011, Ethicon's Worldwide Director of Medical Affairs and co-investigators validated the inferiority of it TVT-SECUR product compared to its TVT-O product. Ongoing prospective evaluations and meta-analyses continued to validate the inferiority of the TVT-SECUR device. In 2014 the Cochrane group's meta-analysis again

confirmed the findings of inferior efficacy and higher complication rates of single incision slings, noting that "The risk of objective failure was four fold higher with single incision slings". Eighty percent of the analyzed data came from studies that utilized TVT-SECUR as the single incision sling.

Summary Opinion of Efficacy

It is my opinion to a reasonable degree of medical and scientific certainty that:

- The efficacy of the TVT-SECUR device was inferior to other mid-urethral slings.
- Ethicon was aware of the inferior inferior efficacy of its TVT-SECUR device since 2006 yet failed to warn of such inferiority.
- Ethicon was aware that its TVT-SECUR methods (U vs Hammock) had differing efficacy yet failed to warn of such.
- Ethicon's failure to warn of the inferiority of its experimental TVT-SECUR device harmed women.

COMPLICATIONS (ADVERSE EVENTS) SUMMARY

In February of 2008, Dr. Menachem Neuman, one of the world's most experienced TVT-Secur surgeons, emailed Ethicon's World Wide Medical Director, David Robinson, Ethicon's World Wide Marketing Director, Harel Gadot, Ethicon Engineer and first author on the TVT-Secur related patents, Dan Smith, and Ethicon's Director of Research and Development, Scott Ciarrocca.[186] The focus of this email was Dr. Neuman's findings with regard to TVT-S complications. Dr Neuman noted his experience. He had implanted 477 TVT-Secur devices. Dr. Neuman informed Ethicon

[186] ETH.MESH.03923121; See also ETH.MESH.00328895 (Acknowledging that rigid mesh "may increase vaginal stiffness postop with the potential to impair sexual function.")

that, compared to TVT-O, “there were more post operative obstructions, vaginal pain and tape protrusions”.

Dr. Neuman informed Ethicon “Most of the vaginal pain and lateral tape protrusion is caused by the increased tape stiffness - my feeling it is due to the laser cutting”, “TVT-S is attached in general to more operative bleeding than TVT / TVT-O, and requires more force for introduction. The edges should be much thinner and rounder. This will reduce the vaginal wall injury ("button halls") as well”, and “The detachment is not smooth enough , too many un-desired tape removal are reported”.

He added, that based on his experience, it had “become obvious” that the TVT-O and TVT devices were designed by surgeons with attention to anatomy and surgery, whereas the TVT-Secur device had been designed by engineers focused on mesh production and the mechanical insertion mechanism. The email was forwarded Ethicon’s EMEA Director of Marketing, Andrew Beveridge, to Ethicon’s Director of Medical Affairs, Axel Arnaud. That email stated, “lets discuss before taking action”.

Surgical intervention for complications such as pain, dyspareunia, and obstructive symptoms has been shown to result in cure in less than half of all cases.[187] Below is a summary of complications as reported in the review of the literature discussed in detail elsewhere in this monograph.

BLADDER AND OR URETHRAL PERFORATIONS

The high risk of injury to the bladder and unintended trajectories of the TVT-SECUR inserter were initially demonstrated it the pre-market TVT-SECUR Design Validation Study (25% incidence of bladder penetration). In 2009 Hubka et al published

[187] Coskun, Burhan, Rebecca S. Lavelle, Feras Alhalabi, Gary E. Lemack, and Philippe E. Zimmern. "Mini-slings Can Cause Complications." *International Urogynecology Journal*26.4 (2014): 557-62.

its cadaveric evaluation of the TVT-SECUR procedure. In the hands of experienced surgeons, the bladder was entered with 10% of TVT-SECUR passes. Although cadaveric studies are not a replacement for live human trials, this high incidence of bladder perforation is not noted in similar study of other mid-urethral slings.[188] In 2014 Schimpf et al reported that the TVT-SECUR device was more likely than TVT to be associated with urethral perforation (2.7% vs < 1%). In 2014 the Cochrane meta-analysis of single incision slings, based predominantly on TVT-SECUR data, noted The relative risk of erosion into the urethra or bladder was almost 18 times that of other midurethral slings.[189]

Summary Opinion of the TVT-SECUR Risk of Bladder and or Urethral Injury

I state with a reasonable degree of medical certainty that, more likely than not, the TVT-SECUR device is associated with a higher risk of urethral injury than other mid-urethral slings, is associated with a risk of bladder injury and urethral injury that required cystoscopy to be performed at time of both "U" and "Hammock" method implantations, that Ethicon was aware of such these risks yet failed to teach a required cystoscopy at time of such implantation, that Ethicon failed to update its label with warnings of increased risk of bladder and urethral injuries, and that such TVT-SECUR associated risks and failures of Ethicon resulted in harm to women.

RETENTIVE SYMPTOMS

Although there is a small amount of data to suggest the TVT-SECUR device deceased the time to first spontaneous void by minutes (not hours), the meta-analysis of the data found no significant difference between the TVT-SECUR and TVT-O devices.

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[188] Bonnet et al, J Urol. 2005 Apr;173(4):1223-8.

[189] The adverse event profile was significantly worse,specifically consisting of higher risks of vaginal mesh exposure(RR 3.75,95% CI 1.42 to 9.86), bladder/urethral erosion (RR 17.79, 95% CI 1.06 to 298.88) and operative blood loss (mean difference 18.79, 95% CI 3.70 to 33.88).

Summary Opinion of TVT-SECUR and Retentive Symptoms

It is my opinion to a reasonable degree of medical certainty that the TVT-SECUR device provided no reduction in post surgical urinary retention symptoms and therefor provided no such benefit compared to obturator slings.

DYSPAREUNIA

The peer reviewed medical literature demonstrates a de novo dyspareunia rate between 1% and 8%. One of the most experienced TVT_SECUR surgeons in the world, Neuman, reported and 8% incidence of de novo dyspareunia requiring surgical intervention. Meta-analysis has demonstrated a higher incidence of de novo dyspareunia after mini-slings compared to either retropubic or obturator slings.[190]

Summary Opinion of TVT-SECUR and De Novo Dyspareunia

It is my opinion to a reasonable degree of medical certainty that the TVT-SECUR device is associated with a higher incidence of dyspareunia than other mid-urethral slings, that TVT-SECUR related dyspareunia will, more likely than not, not improve without surgical intervention, that Ethicon failed to warn of both the increased risk of dyspareunia and the refractory nature of such, and that Ethicon failed to evaluate such risks prior to commercialization. I state with a reasonable degree of medical certainty that the increased risk of dyspareunia as well as Ethicon's failure to evaluate for such and warn of such has resulted in the harm of women.

POST-OPERATIVE PAIN

The TVT-SECUR may be associated with lower post-operative pain scores. However, the peer reviewed medical literature demonstrates that any such benefit most

[190] Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211:71.e1-27.

commonly is short lived and gone within several days. Additionally, the decrease in post-operative discomfort was not found to be associated with any lower requirement for pain medication. Numerous manuscripts included those that are systematic reviews of the medical literature have note that any such short-term reduction in post-operative discomfort is unlikely to be of clinical or economic significance. The National Institute for Health and Clinical Excellence found that the TVT-SECUR provide less benefit, regarding post-operative reduction in pain, than other mini-slings.

Summary Opinion of TVT-SECUR and Post-Operative Pain

It is my opinion to a reasonable degree of medical certainty that, more likely than not, the short term reduction in post-operative discomfort associated with the TVT-SECUR device is not of clinical significance and that other mini-slings are more likely to provide a reduction in such pain.

EROSION

Reports of high TVT-SECUR erosion rates began in 2007. The rate of TVT-SECUR erosion has been reported to be between 2% and 19%. Meta-analysis has demonstrated a TVT-SECUR erosion rate ranging for 2.4% to 15.2%. In 2008, Piet Hinoul, Ethicon's Worldwide Director of Medical Affairs, performed an RCT that found a 7.3% incidence of TVT-SECUR erosion and a 1% incidence of TVT-O erosion. Considering a 35% loss to follow-up, the erosion rate of TVT-SECUR may have been as high as 29%. Hinoul et al noted a 7% re-operation rate for TVT-SECUR erosion. Both individual RCTs and meta-analyses have demonstrated the risk of TVT-SECUR erosion to be significantly higher than other mid-urethral slings. The systematic review of the literature by the Cochrane group found that the relative risk of erosion with mini-slings to

be almost 4 times that of other midurethral slings.[191] The incidence of mesh exposure with TVT-S was found to be 6% compared 1% with TVT-O. The National Institute for Health and Clinical Excellence (NICE) found that the increased risk of mini-sling erosion disappeared once it excluded the TVT-SECUR device from its meta-analysis.[192]

Summary Opinion of TVT-SECUR and Post-Operative Pain

It is my opnion to reasonable degree of medical certainty that the experimental TVT-SECUR device is associated with a risk of erosion significantly higher than that of other mid-urethral slings and a risk of erosion higher than other mini-slings. I state with a reasonable degree of certainty that Ethicon failed to warn of such increased risk and that such resulted in harm to women. I state with a reasonable degree of medical certainty that Ethicon had reason to believe that its TVT-SECUR method could be modified to reduce the risk of erosion, did not update its IFU with this information, and that it is more likely than not that such failure resulted in harm to women.

HEMORRHAGE-BLEEDING

TVT-SECUR associated intraoperative hemorrhage has been reported to occur in as many as 4.5% of TVT-SECUR "hammock method" cases. In 2009 Ethicon's Worldwide Director of Medical Affairs, Peit Hinoul and co-investigators published their RCT findings (TVT-SECUR vs. TVT-O). These findings demonstrated the that there was significantly more blood loss associated with implantation of the TVT-SECUR device. In 2014 the Cochrane groups meta-analysis validated the findings of Hinoul, finding that mini-slings were associated with significantly more blood loss than other mid-urethral

[191] The adverse event profile was significantly worse,specifically consisting of higher risks of vaginal mesh exposure(RR 3.75,95% CI 1.42 to 9.86), bladder/urethral erosion (RR 17.79, 95% CI 1.06 to 298.88) and operative blood loss (mean difference 18.79, 95% CI 3.70 to 33.88).

[192] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 566. Single-incision short sling mesh insertion for stress urinary incontinence in women. October 2016. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG566

slings. The majority of the Cochrane data was TVT-SECUR data. Hubka et al demonstrated that the TVT-SECUR device and method resulted in a dangerous passage of the TVT-SECUR inserter. The inserter was found to pass within 5 millimeters of the blood supply of the obturator internus muscle, the "nutritive artery". The authors noted, *"As we have documented, haemorrhagic complication can be caused by the nutritive artery of the obturator internus muscle*". As noted previously herein, the TVT-SECUR is associated with a high incidence of erosion. *Ethicon's TVT-SECUR expert witness, Dr. Jaime Sepulveda has opined that the increased risk of bleeding is associated with the increased risk of erosion.*[193]

Summary Opinion of TVT-SECUR and Hemorrhage-Bleeding

I state with a reasonable degree of medical certainty that the experimental TVT-SECUR device and method is associated with a risk of bleeding that is significantly higher than that of other mid-urethral slings, that Ethicon failed to assess the relationship of its TVT-SECUR device to the blood supply of the obturator internus muscle before or after marketing the device, that Ethicon failed to warn of its failure to evaluate such anatomic relationship, that Ethicon failed to update its label once this relationship became known, and that such failures resulted in the injury of women.

LENGTH OF SURGERY

Although one of the most experienced TVT-SECUR surgeons in the world, Neuman, found no significant difference in the time required to implant a TVT-SECUR or TVT-O, Hinoul found that the TVT-SECUR could be implanted two minutes quicker.

[193] Expert report of Dr. Jaimie Sepluveda, Wave 3, pg 19

The Cochrane meta-analysis found that single incision slings (mini slings) could be implanted one minute faster than obturator slings and added "reported "the clinical and economic advantages of a one- minute reduction in theatre time are likely to be negligible".

Summary Opinion of TVT-SECUR and Length of Surgery

I state with a reasonable degree of medical certainty that the TVT-SECUR can be implanted 1-2 minutes quicker than transobturator slings and that such reduction of time is unlikely to have resulted in any clinical or economic benefit.

DE NOVO URGE SYMPTOMS

Since 2008 there has been a growing pool of data demonstrating a high incidence of de novo urge and urge incontinence following implantation of the TVT-SECUR device. In 2009 Kroft et al found a 23% incidence of de novo urge incontinence and reported that *"There was a surprisingly high incidence of urge incontinence and mesh erosion"*. In 2011, Walsh et al published their systematic review of the literature on TVT-SECUR outcomes. The authors concluded, *"based on the present study, rates of de novo OAB after a TVT-S procedure do not appear lower, and may indeed be higher, than established MUS techniques"*. That same year, Hinoul et al reported the results of their TVT-SECUR vs. TVT-O randomized controlled trial. Subjective reporting of urgency and/or urge incontinence was noted in 23.3% and 23.0% of patients treated with the TVT SECUR device at 6 months and 1 year vs 16.3% and 16.7% with the TVT-O device, respectively. Also in 2011, Tommaselli et al, presenting the results of their systematic review of the literature, noted that the relative risk of de novo urgency following a single incision sling was approximated double that of standard midurethral slings. In 2014 the

Cochrane group reported the findings of its systematic review of the literature. The authors found that the relative risk of de novo urgency following a single incision sling was 2.39 (CI 1.25 to 4.56) compared to other midurethral slings. Compared to bottom-up retropubic slings, the TVT-SECUR was associated with more than two times the risk of de novo urgency. In 2016, The National Institute for Health and Clinical Excellence (NICE) reported on their meta-analysis. NICE found that de novo OAB symptoms were significantly higher at five years after single incision sling implantation compared to other mid-urethral slings.

Summary Opinion of TVT-SECUR and De Novo Urge Symptoms

I state with a reasonable degree of medical certainty that the experimental TVT-SECUR device is associated with a risk of de novo urge symptoms that is higher than that of other midurethral slings and that the effects of such risk are more likely than not, to persist in perpetuity. I state with a reasonable degree of medical certainty that Ethicon failed to evaluate this risk prior to commercialization of its experimental TVT-SECUR device and failed to warn of such. I state with a reasonable degree of medical certainty that this failure by Ethicon resulted in the harm of women.

RESURGERY

Since 2009 there has been a growing pool of data demonstrating the remarkably high re-surgery rate (repeat surgery rate) associated with the experimental TVT-SECUR device. In 2010 Cornu et al reported a 27% rate of repeat surgery to treat recurrent or persistent SUI. In 2011 Ethicon Worldwide Director of Medical Affairs and co-

investigators reported on the results of their TVT-SECUR vs. TVT-O randomized controlled trial. They noted that 15% of TVT-SECUR patients had undergone or were scheduled to undergo resurgery for persistent or recurrent SUI. That same year, one of the world's most experienced TVT-SECUR surgeons, Neuman, reported an 8% re-surgery rate for persistent dyspareunia. In 2011 a systematic review of the literature by Abdel-Fattah et al found that the relative risk of repeat SUI surgery following a single incision sling was almost seven fold that of standard midurethral slings. In 2012 an Ethicon's internal document demonstrated its awareness of the high resurgery rate associated with its TVT-SECUR device, *"[T]he TVT-Secur product is associated with inferior patient-reported and objective cure rates at 1 year, and higher reoperation rates when compared to standard mid urethral slings (e.g. TVT TM /TVT-O TM).."*.[194] In 2014 the Cochrane group reported the results of it systematic review. The authors noted that, compared to "in to out" obturator midurethral slings as well as all obturator slings (as a group), repeat surgery for SUI was six times more likely with a single incision sling. Additionally, the authors found that the TVT-S device was associated with a 2.5 fold increased risk of additional surgery for complications (statistically significant). In 2016, The meta-analysis of National Institute for Health and Clinical Excellence would find that, by excluding the TVT-SECUR data, the rate of repeat continence surgery following single incision slings was not statistically significantly from other mid-urethral slings.[195]

Summary Opinion of TVT-SECUR and Resurgery

I state with a reasonable degree of medical certainty that the implantation of the experimental TVT-SECUR device results in a higher incidence of resurgery compared to

[194] ETH.MESH.05600922
[195] National Institute for Health and Clinical Excellence. Interventional procedure guidance 566. Single-incision short sling mesh insertion for stress urinary incontinence in women. October 2016. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG566

other mid-urethral slings including other single incision slings, that Ethicon failed to evaluate the risk of resurgery prior to commercialization of its TVT-SECUR device, that Ethicon failed to inform that it had not evaluated this risk, and that such failure of Ethicon has harmed women.

QUALITY OF LIFE

Although individual studies have shown an improved quality of life score following TVT-SECUR implantation, meta-analysis has found not QOL benefit compared to other mid-urethral slings. However, the Cochrane group did find that quality of life was significantly better after the bottom-up retropubic sling compared to SIS. Four of the five trials evaluated were TVT-SECUR trials.

Summary Opinion of TVT-SECUR and Quality of Life

I state with a reasonable degree of medical certainty that the TVT-SECUR offers not quality of life benefit compared to other mid-urethral slings and, more likely than not, offers a lower quality of life than the TVT bottom-up sling.

The 522 Order

In January of 2012 the FDA issued a 522 order to Ethicon. This order required post market surveillance of multiple mesh products including the TVT-Secur product. Ethicon's internal document, Background Information on the TVT SECUR, memorialized Ethicon's response.[196] This document noted, "While the TVT-Secur product is associated with inferior patient-reported and objective cure rates at 1 year, and higher reoperation rates when compared to standard mid urethral slings (e.g. TVT TM /TVT-O), Ethicon has concluded that the minimally-invasive procedure using TVT-

[196] ETH.MESH.05600922

Secur is an acceptable choice of therapy for a carefully selected patient population when implanted by experienced surgeon".

This document further noted, "Ethicon notified FDA's Office of Surveillance and Biometrics on May 9, 2012 that, based on a commercial decision, Ethicon would stop selling the following products (TVT-S included) within 120 days from the date of the notice. We also stated that Ethicon had no intention of commercializing these products in the future. Ethicon requested, therefore, that FDA place the 522 orders for these products on hold".

On May 2nd of 2012, Ethicon notified the FDA that it would stop commercializing the TVT Secur device.[197] On June 1st of 2012 Ethicon created its internal template, Ethicon GYNECARE Worldwide Commercialization Decision.[198] This template was marked "CONFIDENTIAL. NOT FOR DISTRIBUTION". Ethicon therein notes that, even though the 522 order for post-market surveillance applies only in the USA, they would be discontinuing the TVT-SECUR worldwide. Ethicon noted it had no plans to return TVT-S to market.

Summary Opinion of Ethicon's Response to the 522 Order

As noted throughout this monograph and confirmed in this internal Ethicon document, the TVT-SECUR device was associated with lower efficacy and higher complication rates compared other midurethral slings. Based on the findings discussed in detail throughout this monograph, I state with a reasonable degree of medical and medical device industry certainty, that Ethicon's decision to terminate the manufacturing

[197] ETH.MESH.04474313
[198] ETH.MESH.07316987

and sales of its TVT-SECUR device throughout the universe was secondary to the defective nature of the device, the method of the device, and a failure to achieve its primary objective through the device, recapture market share and maintain revenue.

The Method and Method Sections of The IFU Were Defective

Dr. David Robinson, Ethicon's Worldwide Medical Director has noted, with regard to the TVT-SECUR procedure, "It is critical that the steps in the IFU be followed precisely".[199]

Axel Arnaud, Worldwide Director of Medical Affairs, in an email chain involving David Robinson and the TVT-SECUR Project Lead, noted:

> The reality of the field is that some surgeons, including KOL's who have been correctly trained and who have passed the learning phase, are raising concerns about the efficacy of TVT Secur. They have hard time to achieve consistently good results with the device. They are asking for clear recommendations about the way to perform the procedure.[200]

In December of 2006, shortly after product launch, Ethicon's Director of Medical Affairs, Axel Arnaud, emailed Ethicon's Worldwide Director of Medical Affairs, Dr. David Robinson, and Ethicon's TVT-S Project leader and TVT-S inventor Dan Smith, a "Cookbook" with improved procedural instructions.[201] Axel noted that the content of this document was derived from the observing the surgeries of experts, discussions with experts, from European expert panels, as well as pearls from U.S. surgeons. Axel recommended that these improved instructions be validated by 3 US and 3 European surgeons with good TVT-S experience and then reviewed by regulatory affairs. Although

[199] ETH.MESH.03179016
[200] ETH.MESH.01784428
[201] ETH.MESH.01784434

the document appears to have been well received by Dr. Robinson, Mr. Smith, the inventor and project leader, seemed to take offence. Mr. Smith replied,

> *"Everything in Blue shading is either wrong or needs much work to align with the IFU and I am not rewriting another IFU"*
>
> *"The IFU contains the detail information which they MUST follow, this document should be a cheat sheet, not another IFU".*
>
> *"Sorry to rain on your parade"*[202]

Axel Arnaud, Ethicon's Director of Medical Affairs replied back to Ethicon Engineer and Product Lead,

> I have hard time to understand how you can state what is wrong or right, what MUST be followed or not, what is needed or not when many of our customers themselves still do not know after their initial experience with TVT Secur.[203]
>
> The documents I sent you are based on the opinion of numerous European experts and pearls from US surgeons. Thus ,they cannot be qualified as "wrong", in particular based on the fact that they differ from the IFU.
> Axel is stating what seems to be obvious, Dan Smith is an engineer, not a

surgeon. The existing IFU was developed without the benefit of clinical trials and resultant surgeon input. Axel Arnaud finds it unlikely that an engineer who has never done the surgery believes that he knows better then surgeons who are performing the surgery. The response of Mr. Smith seem to represent arrogance and defensiveness from an inventor of the TVT-S device. Axel continued his response,

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[202] ETH.MESH.01784433
[203] ETH.MESH.01784432-33

> The reality of the field is that some surgeons, including KOL's who have been correctly trained and who have passed the learning phase, are raising concerns about the efficacy of TVT Secur. They have hard time to achieve consistently good results with the device. They are asking for clear recommendations about the way to perform the procedure, in particular about the size of the dissection, the tension to be given to the tape and the way to perform a cough test. If you disagree that these are not the critical elements to achieve positive outcomes, please let me know urgently which they are.
>
> The answers to the surgeon's questions not being in the IFU, there is a need for what made the reproducibility and success of both TVT and TVT-O i.e. a "cookbook".

Dan Smith responded to this email from Axel, stating that Axel could create a new IFU based on his finding as long as he followed standard U.S. Design Controls to validate the new IFU. Consistent with the messaging of David Robinson, that the IFU must be followed precisely, Mr. Smith added, “We can NOT have a cookbook that differ from the package insert”.

Axel Arnaud concluded,

> Thus, to summarize, I suggest that we keep on working together with Dave on the cookbooks and keep in mind that a revision of the IFU might be needed.[204]

Demonstrating his reluctance to update the his original IFU, the IFU created prior to the first clinical use of the device, Dan Smith responded,

> Based on your strong position as stated in bullet#4 above to rewrite the TVT SECUR IFU, I will unfortunately need to remove myself from this project, due to the limited time I have to support this effort. Therefore I wish you much success in the noble endeavor, and I will try to make myself available on a limited basis to answer any questions your new team may have.

[204] ETH.MESH.01784431

Ethicon's Worldwide Medical Director, David Robinson, intervened with the following response, "[L]et us get a plan together than incorporates corrective action that is understandable by the surgeon and can be put in the field expeditiously".

In November of 2006, Ethicon's Great Britain Country Directory, Ralf Gotter, emailed Ethicon's European Marketing Manager and Ethicon's Worldwide Director of Medical Affairs. The Subject of the email was "The more procedures the more problems". In this email, Mr. Gotter reported "We see no correlation with training hospitals or regions. Problems appeared in both. Hammock and U-position" and Please let me know your ideas. As soon as a cook book or an international summary on tips and tricks is ready we would be happy to use it immediately".[205]

Ethicon's internal marketing document "Procedural Pearls & Frequently Asked Questions" describes numerous problems with the TVT-Method and offers solutions. [206] However the IFU was never updated to reflect the herein noted solutions or teachings. Indeed, the document is marked, "Do not distribute – Internal Use Only" and, "The information on the use of GYNECARE TVTS SECUR System by the surgeons referred to in the document is not intended to be used as a surgical training guide. An internal document provides Ethicon's rationale for not providing physicians of the world with this important label. This document indicates that the dissemination of such information would be seen as a safety alert,

'*This would be seen most likely as a safety alert. Right now, we think this is how we need to approach Australia, but we need to confirm this and also better understand the global implications of this, especially in light of the data we're getting in item #2* (the new label)".[207]

[205] ETH.MESH.03921612
[206] ETH.MESH.00157010

[207] ETH.MESH.00874519

The discussion of method and IFU defects that follows presents of the questions and solutions offered by this document.

Of additional concern, Ethicon herein has acknowledged that expert surgeons were having difficulty with the TVT-SECUR procedure and its expert, Dr. Brian Flynn, has opined that the TVT-SECUR was designed for use by the non-experts in the community.[208]

The Insertion Method

In 2006, answering the question as to why the mesh was coming "undone" during inserter withdrawal, Ethicon's Worldwide Medical Director noted that there was a "technical flaw".[209]

Why is it difficult to get the inserter off at the end of the procedure?

Solutions offered in the confidential document:

> The correct method is to slightly twist it to-45 degrees THEN start to gently pull the inserter out. The inserter can also be twisted to the opposite -45 degree and THEN the process of gently pulling is repeated until the inserter is free from the implant. If the inserter is not yet free, you should only be pulling the inserter out in the same path it was inserted while the inserter is canted on one edge. This helps the device to be released from the spring in the inserter.

If this fails, two other solutions are offered:

> Another technique found to be helpful is to push the inserter forward slightly for 1mm AFTER the wire has been pulled.

> Dr. Lucente has also found the placement of a very narrow malleable retractor (such as those used in ENT surgery) between the mesh and the inserter to be helpful in creating stability for the mesh while removing the inserter.

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[208] TVT-SECUR expert opinion of Dr. Brian Flynn pg 52
[209] ETH.MESH.03179016

> Tip: Only remove ONE inserter at a time and check mesh placement (cough test can be used in between each inserter removal). This may improve results.

None of the above appeared in the IFU, which taught only "GENTLY REMOVE the *inserter* the incision after the release wire hits its 'stop'. A slight twisting motion of the *Inserter* will assist in this maneuver. NOTE DO NOT FORCE the removal of the *Inserter,* as it may change the implant position or cause the implant end to be removed. If force is needed, reconfirm release wire has been pulled to its 'stop' position and then GENTLY SLIDE the *Inserter* out using a slight twisting motion".

In November of 2006, Ethicon's Great Britain Country Directory, Ralf Gotter, emailed Ethicon's Europian Marketing Manager and Ethicon's Worldwide Director of Medical Affairs. The Subject of the email was "The more procedures the more problems". In this email, Mr. Gotter reported "I would like to inform you that we are facing some problems within the last day with TVT SECUR. Strong bleeding and or haematoma in 5 cases, Inserter removal with fixation tip in 4 cases, Failures (not continent) in 4 cases. We see no correlation with training hospitals or regions. Problems appeared in both. Hammock and U-position".[210]

Why would the mesh get loose after pulling the release wire?"

Solutions offered in the confidential document:

> "It is very important that you keep a tight grasp on the inserter while releasing the wire. If the inserter is not held in place when the wire is pulled towards the surgeon, there is a possibility that the inserter will start to pull out as well".
>
> None of the above appeared in the IFU, which taught only "When satisfied with the FINAL mesh positioning, release one *Inserter* from the *Device* by pulling the release wire (item Fof FIGURE 1) while stabilizing the *Inserter [see* FIGURE 14). NOTE - The *Device* and *Inserter* cannot be reattached after the release wire

[210] ETH.MESH.03921612

> is pulled. The release wire must be pulled completely to its 'stop' position in the Finger Pad to separate the Inserter from the *Device.* To facilitate the implant release, pull the wire using a needle driver/holder, hemostat or forceps".
> Although the IFU does teach "stabilizing" the inserter, it teaches neither "tight grasp" nor the consequences of not utilizing a "tight grasp".

It should also be noted that in the Original Part of Ethicon's 2004 TVT-S design validation study, there was a 25% incidence of inserter trouble in removing the inserter without dislodging the TVT-S sling.[211] Ethicon's solution was to BOLD FONT the sentence in the IFU that described the inserter removal. As described elsewhere here in, they failed to validate that this BOLD FONT corrected the inherent flaw of this procedural step. In Parts 2 and 3 of this validation study, there was a 33% incidence of problems with the use of the release wire.

"Even though the lateral incisions are wide, the shape of the inserter (not being a needle) makes it difficult to fit in the preformed canal".

Solutions offered in the confidential document:

"If you can get the tip of your finger into the tract and touch the ramus or lower edge of the pubic bone, then you know the tract is open enough".

The importance of this wider dissection would later be espoused by Ethicon KOL, Dr. Neuman who noted "The inserters, being more than twice as wide as TVT and TVT-obturator needles, necessitate wider tunnels, 12 mm at least, to permit smooth passage of the tape and inserter and to avoid gathering of vaginal skin, which may lead to vaginal wall penetration.[212]

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[211] ETH.MESH.00325950

[212] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

None of the above appeared in the IFU, which taught only "After initiating sharp dissection, continue with a small pair of blunt scissors, making two small paraurethral dissections (approximately 1.0 cm). The typical index finger is wider than 1.0 cm and the tract created by an index finger will dilate the linear dissection circumferentially.

In 2008 Neuman, one of the most experienced TVT-Secur surgeons in the world, opined that the TVT-SECUR method taught in the IFU was defective.[213] Neuman modified the method. Many key opinion leaders performing prospective clinical trial subsequently used this method. Ethicon's internal documentation describes the modifications of Neuman, yet Ethicon did not update its instructions for use to reflect such.[214] Neuman's method included widening the incision beyond the 10mm taught in the iFU, "made wide to 12 to 15 mm' by spreading the scissors blades while withdrawing it,at a plan parallel to the vaginal wall". Ethicon did not update its IFU with the widened incision for its inserter.

The method of inserter removal was so difficult to understand and perform that an Ethicon TVT-SECUR professional education slide dedicated 16 of 29 procedural slides to removal of the inserter. Only 3 of 29 slides were used to teach insertion of the inserter.[215]

Of additional note, Ethicon TVT-SECUR Project Lead, Engineer, and inventor noted the following key design input in his initial TVT-SECUR proposal,

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[213] Neuman, M., Perioperative Complications and Early Follow-up with 100 TVT-SECUR Procedures. Journal of Minimally Invasive Gynecology (2008) 15, 480-484
[214] ETH.MESH.02320488
[215] ETH.03472421

"The delivery device will provide the surgeon with a safe, easy to use, reproducible and anatomically designed instrument for implant insertion, placement and adjustment from the vaginal incision".[216]

Summary Opinion of Inserter Method and IFU

I state with a reasonable degree of medical certainty and medical device industry certainty that the TVT-SECUR insertion method was defective, the pre-launch Device Design validation demonstrated a defective insertion method, the post-market experimentation on the women of the world demonstrated the insertion method do be defective, Ethicon was aware of such defectiveness yet failed to either update it IFU to inform and warn rendering its IFU defective, Ethicon fialed suspend marketing pending corrective action, and that such resulted in harm to women.

The Tensioning Method

"How much tensioning should be applied to the GYNECARE TVT SECUR System tape?"

Solutions offered in the confidential document:

"You may need to place GYNECARE TVT SECUR Hammock even tighter than GYNECARE TVT Obturator System because the tape lies flatter and the loads applied to the urethra are distributed out over a larger surface area, which further reduces the potential for retention".

"Tensioning on the mesh should be enough that a small instrument may be placed between tape and urethra without elevating the urethra".

None of the above appeared in the IFU, which taught only "Disconnect the needle driver/holder to assess the tension-free mesh placement under the mid urethra. Make final

[216] ETH.MESH.07898861

adjustments if needed by reconnecting the needle driver/holder and establishing proper hand position to ensure the *Inserter* tip remains in contact with the bone. Advance or retract the patient's left or right side *Inserter,* depending on the insertion depth of each *Inserter.* NOTE - You may use the markings on the *Inserter* or the distal end of the *Inserter* to aid in appropriate positioning" and "Assess the positioning of tension-free tape, (i.e., cough test or other means). NOTE - Adjustment of the *Device* to achieve tension-free placement should be made by moving the *Inserters*- NOT by pulling on the mesh, NOTE - The final position of the *Inserters* should be similar but do not need to be symmetrical (see FIGURE 13). NOTE - If either end of the *Device/lnserteris* placed and then removed and Inserted In a second location, the surgeon should ensure that the mesh is securely fixated under the urethra during the final assessment of the tension-free placement.

In the 2005 Device Validation Study 13 surgeons performed the TVT-S surgery. The validation questionnaires from 2 of 13 were lost. Of the remaining 11 experts, Dr. Daniele Grassi noted that the sling was too loose and commented, "TVT-S will require a different approach to tensioning the implant as compared to regular TVT and TVT-O. This is due to the fact that you do not need to remove any sheath nor allow slack for tightening the implant as the sheath is removed".[217] Her comments were not reflected in any update to the IFU.

"Can the tape tension be adjusted?"

Solutions offered in the confidential document:

> "Refer to the IFU for detailed instructions. Adjustment is done by grasping an inserter with the needle holder, achieving proper hand position and either advancing or withdrawing that inserter. First, consider which is the most

[217] ETH.MESH.00325956

> appropriate inserter to move, if the mesh is too tight, withdraw the inserter that IS inserted deeper, if the mesh is too loose advance the inserter that IS NOT inserted as far. It is very important to ONLY release one inserter at a time after the FINAL mesh position is achieved. After release and removal of the 1st inserter, reconfirm the FINAL mesh position. This is done again because there is greater visibility and the mesh cannot be tightened after implant release".

None of the above appeared in the IFU, which taught only "Adjustment of the *Device to* achieve tension-free placement should be made by moving the *Inserters* - NOT by pulling on the mesh", "If adjustment to the FINAL mesh position is needed, adjust the mesh tension with the remaining inserter BEFORE pulling the release wire" and "The *Device* and *Inserter* cannot be reattached after the release wire is pulled". The IFU does not teach the full adjustment method. The IFU fails to warn that the mesh cannot be tightened after implant release. Furthermore, the IFU fails to teach a reproducible method of tensioning and Ethicon knew that surgeons will be predisposed to incorrect tensioning. Ethicon's engineer and an inventor of the TVT-Secur sling noted, when describing the laser cut nature of the prototype MiniMe sling, "TVT-O MC (mechanically cut) is used, by more than 90% of all TVT-O user! This means that as TVT-O users are converted they will have early failures as did TVT SECUR until they figure out that a mini-sling needs to be placed differently (tighter) due to the mesh properties" (laser cut).[218]

"Can the tape tension be loosened after I have released the implant?"

Solutions offered in the confidential document:

> "If a LOOSENING adjustment is required AFTER releasing the implants, CAREFULLY grasp the base of the implant fixation end on one side with a needle holder. Then gently pull the end downward. DO NOT pull on the center of the mesh implant as with conventional over-correction methods. This method for over-correction should only be done as a last resort. An implant left too loose after removal of the inserters or pulled out during as described above will require implant removal and use of a new properly placed device".

[218] ETH.MESH.09911297

None of the above appeared in the IFU, which provided no method for fixing an overcorrection (tight sling). Without provision of this teaching noted herein, it would be natural for a surgeon to treat overcorrection as he or she does with other mid-urethral slings, a method herein warned against. The failure of Ethicon to teach this warning in its IFU, more likely than not, resulted in surgical failures.

"Can the device be adjusted once in position?"

Solutions offered: "The GYNECARE TVT SECUR can and should be adjusted to ensure proper outcomes before the inserters are detached from the implant. Refer to the IFU for detailed instructions. An implant left too loose after removal of the inserters will require implant removal and use of a new properly placed device. The implant needs to be completely removed by grasping it firmly, removing , and discarding it. It is the surgeon's choice whether to repeat the implant position or choose an alternate location. It is NOT recommended that the inserter be: inserted / removed/ inserted/ removed and reinserted using the same approach ("U"or"H"). In this rare case an alternate pathway or device such as GYNECARE TVT and GYNECARE TVT Obturator should be advised to achieve adequate initial fixation."

This teaching did not appear in the IFU. Herein Ethicon is teaching its representatives that implant removal is required if the implant is loose. However, this important teaching was not added to the instructions for use. Furthermore, it teaches not to repeat the same method. This teaching was also missing from the IFU. It also herein provides misleading and confusing teaching. It provides that there will be rare cases that an alternative pathway is advised. It does not define these "rare cases". Additionally, such

cases of surgeons needing to use a second TVT-S or choose an alternative pathway were common in the prospective evaluations that followed (2.6 to 8.8% incidence).[219]

In 2007, Ethicon was informed that the most important Key Opinion Leader in British Columbia thought the TVT-S was a "crappy device". This comment was predicated on issues with tensioning. The B.C. sales representative noted, "I was in a case with him yesterday where he did a hammock, at cough test she leaked & he couldn't tighten it enough to stop the leaking. He then did a 'U', same thing. He then did a Monarc-perfect! It was very frustrating & at the end of the case he told me that he thought SECUR was just a 'crappy' device".[220]

In 2007 Ethicon was informed by its Australian Key Opinion Leader, Professor Frazer, "*the IFU is fundamentally misleading. Tension-free, tension-less and placement with no tension are complete misnome*rs."[221] Ethicon's Australian Medical Director noted that Dr. Frazer "said the document states that the device should be placed beneath the urethra and barely in contact with the urethra, but that "the company is now suggesting that it should be much tighter than it states, because you assume it (the mesh)., or the tissues may loosen" and "Regarding the revised Key Technical Points document, he said that "*the section on tensioning is inadequate*" in his opinion. It is "still not as clear as it could be." He described the blue diagram as "confusing" and said there appeared to be "*contradictory or confusing statements on tension*" within the body of the text."[222]

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[219] Tommaselli, Giovanni A., Alessandro Dâ™Afiero, Costantino Di Carlo, Carmen Formisano, Annamaria Fabozzi, and Carmine Nappi. "Tension-Free Vaginal Tape-O and -Secur for the Treatment of Stress Urinary Incontinence: A Thirty-SixMonth Follow-Up Single-Blind, Double-Arm, Randomized Study." *Journal of Minimally Invasive Gynecology* 20.2 (2013): 198-204, Barber, Matthew D., Alison C. Weidner, Andrew I. Sokol, Cindy L. Amundsen, J. Eric Jelovsek, Mickey M. Karram, Mark Ellerkmann, Charles R. Rardin, Cheryl B. Iglesia, and Marc Toglia. "Single-Incision Mini-Sling Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence." *Obstetrics & Gynecology* 119.2, Part 1 (2012): 328-37.

[220] ETH.MESH.00811032

[221] ETH.MESH.00327061

[222] ETH.MESH.00327061

In 2008 Neuman, one of the most experienced TVT-Secur surgeons in the world, opined that Ethicon's TVT-SECUR IFU method was defective.[223] Dr. Neuman described the need for increased tension. "The tape tension should be a little bit more than for the TVT and TVTO, to be at close proximity with the Urethra, while not causing it to bend. The cough test might be used for fine tuning of the tape tension".

Ethicon's internal documentation describes the modifications of Neuman, yet Ethicon did neither updated its instructions for use to reflect such nor did the requisite RCT to validate the modifications of Neuman.[224]

In 2008 Martan et al reported "The tape used in the TVT-S procedure is less elastic than that used in the TVT or TVT-O procedure, so this tape must be slightly over-tightened, which means the tape is not tension- free. These steps are crucial for the curative effect". Most surgeons have NO idea to the dynamics of the sling, nor that TVT (Tension-free Vaginal Tape) is actually not tension free, and it never was!"[225]

In 2008, Dr. Vince Lucente, Ethicon Key Opinion Leader and International TVT-SECUR trainer, presented his surgical video at IUGA national meeting, TVT Secur Surgical Technique and Learning Tips and Tricks. Dr. Lucente taught "We have found that placement of the TVT SECUR must be tighter against periurethral tissues to ensure optimal dryness as compared to its predecessors". [226]

In 2008, Ethicon engineer and TVT-S inventor, David Smith, noted "Tension of mini-slings is significantly different than what surgeons were used too". "Mini slings

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[223] Neuman, M., Perioperative Complications and Early Follow-up with 100 TVT-SECUR Procedures. Journal of Minimally Invasive Gynecology (2008) 15, 480-484

[224] ETH.MESH.02320488

[225] Martan A, Svabik K, Masata J, El-Haddad R, Koleska T, Pavlikova M
IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

[226] Karram, M; Lucente, V; Khandwala, S; Nilsson, C; Artibani, W; Dmochowski, AN Evaluation Of The Gynecare Tvt Secur* System (Tension-Free Support For Incontinence) For The Treatment Of Stress Urinary Incontinence. Int Urogynecol J (2007) 18 (Suppl 1):S1–S24

have the potential too own a large portion of the market once surgeons understand how to set the tension". "TVT SECUR will NEVER get tighter once placed unlike most other slings to date, because of the short 4 cm of free mesh and laser cut design!" "Although we told surgeons how TVT SECUR needed to be set, they just were not ready to believe us, the sale force was not confident due to early failures, we did not have data to support the thinking, we (Ethicon) never before told surgeons how to set the mesh tension, because there is no one setting!" "Most surgeons have NO idea as to the dynamics of the sling, nor that TVT (Tension-free Vaginal Tape) is actually not tension free, and it never was!". "TVT SECUR will NEVER get tighter once placed unlike most other slings to date."[227] . Smith, when describing the laser cut nature of the prototype MiniMe sling hoped to correct the deficiencies of the TVT-S, "TVT-O MC (mechanically cut) is used, by more than 90% of all TVT-O user! This means that as TVT-O users are converted they will have early failures as did TVT SECUR until they figure out that a mini-sling needs to be placed differently (tighter) due to the mesh properties" (laser cut). Ethicon herein states that they told surgeons how to set the mesh, something they had never done before, because, prior to TVT-S there was no one setting. However, as noted elsewhere herein, the IFU is without of any teachings of how to place tension or that tension should be greater than other methods they had been using. In fact, none of the comments of Mr. Smith noted here were part of that label. Ethicon herein notes that most surgeons do not understanding of the dynamics of this small laser cut sling, yet fail to provide this information in its IFU. Ethicon sling consultant and key opinion leader, Dr. Nilsson, noted "that there was a "strong need for in-procedure test to know the precise adjustment

[227] ETH.MESH.09911296

(tension)".[228] Of additional note, regarding the ongoing development of their next sling, a hybrid of the TVT-S and TVT-O, Mr. Smith noted that they would need to assess how mesh tension will be established across all surgeons.[229]

Ethicon did not update its IFU to include the tensioning described by TVT inventor David Smith or the guidance of its key opinion leaders.

Dr. Jaime Sepulveda, an Ethicon TVT-SECUR instructor, used an Ethicon professional education slide deck that taught a potentially reproducible tensioning method. "Direct visualization of the tape flushed to the urethra fitted snuggly enough to produce a pillowing effect".[230] Although this is an ambiguous teaching, the professional education slide resolves this by defining "pillowing", "Pillowing is described as filling the tape pores with suburethral tissue underneath". The slide deck provides photographs of pillowing. This same method and description appears in what appears to be an internal, Ethicon sales representative, educational presentation.[231] Both the of these documents also offered another tensioning method, "dynamic assessment" (Bladder filled to 200-350 cc followed by cough or crede with sequential tensioning until no more leakage).

These non-ambiguous and perhaps reproducible tensioning descriptions was never added to the IFU and I can find no evidence to suggest it was distributed to the thousands of surgeons worldwide who struggled with the procedure.

The most common effects of inadequate tension with the TVT-SECUR device is, more likely than not, failure to achieve continence. Ethicon's TVT-SECUR expert witness, Dr. Brian Flynn points out a much more grave consequence. Dr. Flynn opines, in his TVT-SECUR expert opinion, that improper tensioning is the route cause of chronic

[228] **ETH.MESH.04048515**
[229] ETH.MESH.09911298
[230] ETH.MESH.03472421
[231] ETH.MESH.00789746

TVT-SECUR urinary tract perforations and TVT-SECUR related fistulae, severe complications.[232]

Summary Opinion of Tensioning Method and IFU

I state with a reasonable degree of medical certainty the TVT-SECUR insertion method was defective, Ethicon was aware of such defectiveness yet failed to either update it IFU to inform and warn rendering its IFU defective, and that Ethicon failed to suspend marketing pending corrective action, and that such resulted in harm to women.

The Dissection Method

"Should doctors dissect beyond the bone?"

Solutions offered in the confidential document:

> "No, the dissection tract should only go to the bone, not beyond in either the "U" or Hammock procedures. Unlike GYNECARE TVT Obturator System, perforation of the obturator internus with scissors is not required".

Ethicon Key Opinion Leader, Dr. Neuman opined the same, "The tunnel depth should not go beyond the bone edge to avoid damaging the tissue meant to hold the coated tape edge; otherwise the tape initial pull-out force might be impaired.[233]

None of the above appeared in the IFU, which taught only "After initiating sharp dissection, continue with a small pair of blunt scissors, making two small paraurethral dissections (approximately 1.0 cml. NOTE - These dissections can be made directionally aligned with the surgeon's choice of either the "U" (at 45° from the sagittal midline) or "Hammock" (9 and 3 o'clock positions or parallel to the floor) approaches described below". As many surgeons performing the TVT-S procedure were experienced with the

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[232] TVT-SECUR expert opinion of Dr. Brian Flynn pg 44

[233] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

TVT-O procedure, the absence of the teaching "Unlike GYNECARE TVT Obturator System, perforation of the obturator internus with scissors is not required" was more likely than not to have resulted in injury and loss of efficacy.

Summary Opinion of Dissection Method and IFU

I state with a reasonable degree of medical certainty that the TVT-SECUR dissection method was defective, Ethicon was aware of such defectiveness yet failed to either update it IFU to inform and warn or suspend marketing pending corrective action rendering its IFU defective, and that such resulted in harm to women.

Cystoscopy

"Do you recommend a cystoscopy when performing GYNECARE TVT SECUR?"

Answer offered in the confidential document: "When GYNECARE TVT SECUR is used in the "U" approach, cystoscopy is REQUIRED - When GYNECARE TVT SECUR is used in the "H" (or Hammock) approach, cystoscopy is OPTIONAL and at the discretion of the surgeon".

This appeared in the IFU. However, Ethicon had not performed the requisite IDE and or observational trials to evaluate the risk of bladder and urethral injury. Ethicon's pre-market device validation trial realized a 25% rate of bladder injur with the "H" method. Subsequent cadaveric study would demonstrate up to a 10% risk of bladder injury with the "H" method. The 2014 Cochrane review would demonstrate an 18 fold relative risk of bladder or urethral erosion for TVT-S compared to TVT-O.[234] It is unknown how many women have undiagnosed TVT-SECUR mesh in the bladder or

[234] Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88., Nambiar A, Cody jD, jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Databaseof Systematic Reviews*2014, Issue 6. Art. No.: CD008709. DOl: 1O.1002/14651858.CD008709.pub2.

urethra. Coskun et al noted that 50% of the their patients with urethral erosions had not undergone a cystoscopy at time of single incision sling placement.[235]

Ethicon's TVT-SECUR expert, Dr. Brian Flynn opines in his TVT-SECUR expert opinion notes *"Intraoperative cystourethroscopy and a thorough physical examination should be performed in all patients undergoing sling surgery. This should be performed in the operating room at the time of mesh insertion to assure that the mesh was placed properly and did not injure the urinary tract or vaginal wall"*. [236] Dr. Flynn continues to opine, *"Mesh erosion (perforation) into the bladder is usually due to an unrecognized bladder perforation at the time of mesh implant or mesh that was inadvertently tunneled in the wall of the urinary tract*" and additionally notes that Ethicon taught cystoscopy was necessary only when performing implantation by way of the "U" method.[237]

Summary Opinion of Cystoscopy and IFU

I state with a reasonable degree of medical certainty that Ethicon's IFU taught that cystoscopy was not necessary when implanting it TVT-SECUR device with the "H" method rendering its IFU defective, that the "H" method was associated with an increased risk of bladder and urethral injury, that Ethicon failed to evaluate such risk prior to commercialization of its TVT-SECUR device, and that it is more likely than not that this teaching or Ethicon has caused women harm.

Performance of Repeat TVT-SECUR Surgery

"Can the GYNECARE TVT SECUR procedure be repeated on a failed case?"

Solutions offered in the confidential document: "Yes, it has the same indications as GYNECARE TVT and GYNECARE TVT Obturator. Since GYNECARE TVT

[235] Coskun, Burhan, Rebecca S. Lavelle, Feras Alhalabi, Gary E. Lemack, and Philippe E. Zimmern. "Mini-slings Can Cause Complications." *International Urogynecology Journal*26.4 (2014): 557-62.
[236] TVT-SECUR expert opinion of Dr. Brian Flynn pg 34
[237] TVT-SECUR expert opinion of Dr. Brian Flynn pg 34,

SECUR is a universal device for either approach, GYNECARE TVT SECUR offers benefits in this situation. Additionally, although not our preferred positioning the "U" approach has greater flexibility in lateral placement of the mesh into the connective tissue and internus muscle, than does GYNECARE TVT".

None of the above appeared in the IFU, which neither provided that the "U" method was not the "preferred positioning" or the reasoning for such. This is of particular interest, as internal documents noted the U method to be more efficacious.[238] Indeed, an Ethicon documentation of an interview with its Key Opinion Leader, Dr. Nilsson, noted that the Hammock method had much lower efficacy than the "U" method.[239] Dr. Nilsson added that the "mini-sling hammock will never work. Furthermore, this teaching encourages the placement of mesh on mesh, a set up for mesh related inflammation, contraction, and related complications such as pain and dyspareunia.

Of perhaps even greater concern, Ethicon had no basis for validating this teaching. Futhermore, Ethicon's pre-market human cadaver study demonstrated a significant decrease in resistance to pull out (urogenital diaphragm) on a second insertion of the device.

Summary Opinion on Repeat TVT-SECUR Surgery

I state with a reasonable degree of medical certainty that Ethicon's taught repeat TVT-SECUR surgery, that it is more likely than not that such is associated with an increased failure rate, that Ethicon failed to evaluate the efficacy of repeat TVT-SECUR surgery providing no basis for such teaching, and that Ethicon's failure to perform such

[238] TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770
[239] ETH.MESH.04048515

testing and failure to inform of the fact that it had not data to support this teaching harmed women.

Patient Positioning

Ethicon's Worldwide Director of Medical Affairs published his cadaveric findings that demonstrated the importance of hip flexion greater then 80 degrees when inserting instrumentation, from in to out, in the direction of the obturator fossa.[240] Although Ethicon did not perform such studies on its TVT-SECUR device, Hubka et al did perform a cadaveric lab that demonstrate that the TVTx instrumentation could come dangerously close to the Obturator nerve (and vessels).[241] It should also be noted that Dr. Neuman, the investigator whose data was relied upon by Ethicon, taught a method that included patient positioning that considered the warnings of Hinoul et al, "Lithotomic classical position, thighs at right angle with the floor, inert high angle of 90 degrees, knees angle - 90 degrees".[242] In direct contradiction to the warnings of Hinoul and the teachings of Delorme, Ethicon trained its representatives to teach positioning physicians to position patients "without hyperflexion".[243]

Although Ethicon would eventually provide a somewhat ambiguous teaching of hip flexion to other TVT product line IFUs, it chose to leave such teaching out of

[240] Hinoul P, Vanormelingen L, Roovers JP, de Jonge E, Smajda S (2007) Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O). Int Urogynecol J Pelvic Floor Dysfunct 18:1201–1206

[241] Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88.

[242] Neuman, M., Perioperative Complications and Early Follow-up with 100 TVT-SECUR Procedures. Journal of Minimally Invasive Gynecology (2008) 15, 480-484

[243] ETH.MESH.00789762

its TVT-S IFU providing only, "Place the patient in the lithotomy position; maintain the table and patient parallel to the floor". [244]

Summary Opinion of Patient Positioning and IFU

I state with a reasonable degree of medical certainty that Ethicon's IFU was defective in that it failed to teach the patient positioning known to move its TVT-SECUR device instrumentation and mesh away from vital structures and that such defect, more likely than not, resulted in harm to women.

The TVT-SECUR Method Fosters Bacterial Contamination, Colonization, Biofilm Formation And Infectious Morbidities

The vulvar skin and suprapubic skin is home to numerous bacteria including staphylococcus, streptococcus, lactobacillus and even MRSA and clostridium. These bacteria are harmless when living on the skin, but can cause grave complications and even death when introduced into the body. The method advocated Ethicon for the implantation of its TVT-SECUR device causes the surgeon to push introducers, PROLENE mesh, and impermeable CODMAN ETHISORB Dura Path through the the contaminated tissues of the vagina. The introducers, microporus mesh, and impermeable CODMAN ETHISORB Dura Path are hence exposed to dangerous bacteria and carry such bacteria into the tissues within the pelvis. As one can easily see, both the tissues and the mesh are at high risk of contamination with dangerous and deadly bacteria. There is ample data demonstrating the bacterial contamination, inflammation and degradation of PPM. This colonization of mesh in the operating field has been shown in several studies and the include single incision implantation method. In 2008, a report of bacterial

[244] ETH.MESH.02340568

analysis of mesh explants by Boulanger showed that bacterial contamination existed to some degree on every explant. In another from 2009, Vollebregt took swab cores from Avaulta mesh implanted during surgery.[245] Over 83% of the 67 samples taken were positive for contamination by vaginal bacteria. Such contamination, they concluded, occurs frequently. In 2013 Shaw et al presented their "*Bacteriological Analysis of Explanted Transvaginal Meshes*". This sample of 50 explants included both prolapse mesh and slings. Fifty two percent of mesh explanted secondary to pain was found to be laden with pathogenic organisms. Eighty-three percent of eroded specimens were contaminated with pathogenic organisms.[246] Bacterial contamination has been shown to worsen the contraction of mesh. Mamy et al found that contaminated mesh contracts four times more than non-contaminated mesh.[247] Thus, it is clear that the transvaginal mesh implantation method is inherently flawed, as the majority of implants shall become contaminated with bacteria capable of degrading the implant, hastening contraction, and causing infection. Indeed the ongoing litigation has revealed a growing number of women who have suffered from severe mesh infections associated with pathogenic skin bacteria.

As noted herein, the transvaginal implantation of polypropylene mesh favors bacterial contamination with resultant potentiating of the PROLENE material defects.

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[245] Vollebregt, A., Troelstra, A,. Van der Vaart, C.H., Bacterial colonisation of collagen-coated polypropylene vaginal mesh: are additional intraoperative sterility procedures useful? Int Urogynecol J (2009) 20:1345–1351

[246] Shah, K., et al., Bateriological Analysis of Explanted Transvaginal Meshes (Abstract 1144).

[247] Mamy, Laurent, Vincent Letouzey, Jean-Philippe Lavigne, Xavier Garric, Jean Gondry, Pierre Mares, and Renaud De Tayrac. "Correlation between Shrinkage and Infection of Implanted Synthetic Meshes Using an Animal Model of Mesh Infection." International Urogynecology Journal Int Urogynecol J 22.1 (2010): 47-52.

The vast majority of transvaginal mesh implants suffer such contamination.[248] When bacteria colonize a foreign body, such as vaginal mesh, it forms a biofilm. "Biofilms are organized communities of microbes typically attached to a surface (either native or abiotic) that display markedly different physiology from free-floating planktonic bacteria, and they are vastly more resistant to antibiotics, they are shielded from host defense mechanisms and they are recalcitrant to ordinary microbiologic culture".[249] Recent investigators have reminded us that biofilms are an important contributor to complications of prosthetic meshes. These investigators found such biofilms on 5 of 5 abdominal meshes explanted for complications.

"Although such infections classically are believed to manifest with low- grade but chronic or recurrent complaints, they also can serve as the source of acute infectious exacerbations, that may arise from detachment of ''planktonic'' bacteria from the biofilm, which are then more able to provoke a fulminant course".

"Biofilms are especially important in chronic infections but also can serve as the nidus from which acute infectious episodes arise as a result of ''showering'' of planktonic bacteria that detach from the biofilm complex".[250]

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[248] Boulanger, Loïc, Malik Boukerrou, Chrystèle Rubod, Pierre Collinet, A. Fruchard, René J. Courcol, and Michel Cosson. "Bacteriological Analysis of Meshes Removed for Complications after Surgical Management of Urinary Incontinence or Pelvic Organ Prolapse.". International Urogynecology Journal Int Urogynecol J. 19.6 (2008): 827-31. Vollebregt, Astrid, Annet Troelstra, and C. Huub Van Der Vaart. "Bacterial Colonisation of Collagen-coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?" International Urogynecology Journal Int Urogynecol J 20.11 (2009): 1345-351. Mamy, Laurent, Vincent Letouzey, Jean-Philippe Lavigne, Xavier Garric, Jean Gondry, Pierre Mares, and Renaud De Tayrac. "Correlation between Shrinkage and Infection of Implanted Synthetic Meshes Using an Animal Model of Mesh Infection." International Urogynecology Journal Int Urogynecol J 22.1 (2010): 47-52.

[249] Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial bio- films: From the natural environment to infectious diseases. Nat Rev Microbiol 2004;2:95–108.

[250] Kathju, Sandeep, Laura Nistico, Rachael Melton-Kreft, Leslie-Ann Lasko, and Paul Stoodley. "Direct Demonstration of Bacterial Biofilms on Prosthetic Mesh after Ventral Herniorrhaphy." Surgical Infections 16.1 (2015): 45-53

The almost universal contamination of transvaginal mesh with resultant bacterial colonization and biofilm formation sets a foundation for chronic waxing and waning inflammation and infectious morbidity. Signs and symptoms of such bacterial colonization and biofilm formation include but are not limited to waxing and waning malaise, myalgia, acute and chronic infections (e.g. UTI) and febrile morbidity. The recalcitrant nature of Biofilms explains the only transient improvement noted with antibiotic treatment. The only effective means of treating biofilm related symptoms is wide excision of the mesh and surrounding tissue. Having treated hundreds of women for transvaginal mesh related morbidities; I have found that site-specific mesh excision rarely results in resolution of recurrent malaise, recurrent UTIs, and febrile morbidity.

It should also be noted that Ethicon knowingly omitted from its TVT-SECUR device a plastic sheathing it believed could decrease bacterial contamination. Ethicon's 2004 provision application filed to protect its TVT-SECUR device stated "A sheath may also allow protection against contamination".[251] Consistent with its belief in the use of sheathing to reduce bacterial contamination of slings, every single one of Ethicon's slings was covered with a plastic sheath. Ethicon's TVT-SECUR expert, Dr. Supulveda, notes in his expert report, "The low risk for infection (TVT) has been attributed to the plastic coated sheaths during its incision.."[252]Although Ethicon stated that it preferred a TVT-S design that would include such a sheath, it opted to exclude such from the commercialized version of its TVT-SECUR device.

[251] USPTO provisional application 60591648
[252] Expert report of Jaime L. Spulveda MD, Wave 3 cases. Pg 18

Summary Opinion of Contamination, Colonization, and Biofilm Formation

I state with a reasonable degree of medical certainty that the defective method of the TVT-SECUR device, more often than not, results in bacterial colonization with worsening contraction of mesh and resultant symptoms, and results in the formation of biofilms with difficult and often impossible to treated infectious morbidities. I state with a reasonable degree of medical certainty that Ethicon knowingly excluded the plastic sheat from its TVT-SECUR device that may have reduced bacterial contamination, colonization, and biofilm formation. *collected in this study show the proof of principle of TVTx and could support the realization of clinical trials with the TVTx mesh*

The TVT-S Method and Device are Associated with Vaginal Dysbiosis, Recurrent Urinary Tract Infections and May Cause Life Threatening Renal Disease.

It has long been known that women with vaginal dysbiosis, characterized by overgrowth of fastidious anaerobes including *Gardnerella vaginalis*, are at higher risk for recurrent urinary tract infections.[253] It has also been demonstrated that transvaginal mesh and mesh erosion is associated with such dysbiosis. I have reviewed tens of cases of women who have suffered from refractory bacterial vaginosis for years, only to eventually be diagnosed with a mesh erosion. The purveyors of transvaginal mesh and slings did not teach of the association of vaginal dysbiosis and the transvaginal implantation of polypropylene mesh. Not only has this resulted in a myriad of women

[253] Sumati AH, Saritha NK (2009) Association of urinary tract infection in women with bacterial vaginosis. J Glob Infect Dis 1: 151–152 , Hillebrand L, Harmanli OH, Whiteman V, Khandelwal M (2002) Urinary tract infections in pregnant women with bacterial vaginosis. Am J Obstet Gynecol 186: 916–917. Harmanli OH, Cheng GY, Nyirjesy P, Chatwani A, Gaughan JP (2000) Urinary tract infections in women with bacterial vaginosis. Obstet Gynecol 95: 710–712. Hooton TM, Fihn SD, Johnson C, Roberts PL, Stamm WE (1989) Association between bacterial vagino- sis and acute cystitis in women using diaphragms. Arch Intern Med 149: 1932–1936.

who have suffered from refractory malodorous anaerobic vaginal discharge but it has resulted in a dramatic increase in the incidence of recurrent UTIs amongst women undergoing such implantation. This increase is most notable amongst the group of women at highest risk for recurrent urinary tract infection, postmenopausal women.

New evidence has validated the link between the defective material of transvaginal mesh and slings and the increased risk of recurrent urinary tract infections. This study has also suggests that the defective mesh may predispose to life threating renal disease.[254] This study found that "[B]ladder exposure to *G. vaginalis* triggers *E. coli* egress from latent bladder reservoirs and enhances the potential for life-threatening outcomes of the resulting *E. coli* UTI" and that even ""Transient *G. vaginalis* exposures were sufficient to cause bladder epithelial apoptosis and exfoliation and interleukin-1-receptor-mediated kidney injury, which persisted after *G. vaginalis* clearance from the urinary tract" . The authors summarized, "Furthermore, upon its exposure to the urinary tract, this vaginal organism (*G. vaginalis)*caused severe kidney damage and other complications, suggesting that carriage of particular vaginal bacteria could also impact a woman's risk for kidney infection. Bladder exposure to *G. vaginalis* is likely to occur during sexual activity in many women".

[254] Gilbert, Nicole M., Valerie P. Oâ™Brien, and Amanda L. Lewis. "Transient Microbiota Exposures Activate Dormant Escherichia Coli Infection in the Bladder and Drive Severe Outcomes of Recurrent Disease." *PLOS Pathogens* 13.3 (2017)

Summary Opinion of Vaginal Dysbiosis and Recurrent Urinary Tract Infections

I state with a reasonable degree of medical certainty that the defective TVT-SECUR method and device caused vaginal dysbiosis, recurrent urinary tract infections, and my be associated with life threatening renal disease.

The TVT-SECUR Method Caused Pain, Dyspareunia, And Visceral Dysfunction.

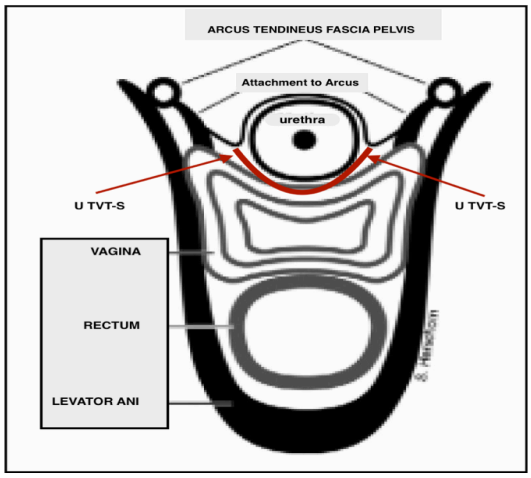
Dr. Charles Butrick, an Ethicon KOL and paid consultant, has stated "The use of muscle sites seems to be intuitively a bad idea, but many of our patients tolerate this non-physiologic but anatomically correct repair without problems. In his recent lecture on chronic pelvic pain given at the Beaumont Chronic Pelvic Pain Conference, Dr. Butrick provided a drawing depicting the sites of "Procedural Induced Myofascial Pain." One such site is the site of TVT-SECUR attachment, the Obturator Internus.[255] Although the most obvious and immediate insult to the pelvic musculature is the direct attachment to or through the levator ani muscles or obturator muscles, such as that taught for the TVT-SECUR "Hammock" method, it is of tantamount importance to recognize that any insult to the anterior vaginal wall tends to cause the same pelvic myofascial pain. This is because the entire anterior vaginal wall and its fibromuscular layer are in direct communication with both the levator ani muscles and the obturator muscles. Dr. Sepulveda, an Ethicon TVT-SECUR instructor, explained the even the "U" method would effect the levator ani muscle group "U Insertion enters into the tendinous insertion of the pubovisceral component of the LEVATOR complex".[256]

[255] Image available upon request
[256] ETH.MESH.03472421

DeLancey et al were amongst the earliest to describe this relationship. They noted that "The urethra lies on a supportive layer that is composed of the endopelvic fascia and the anterior vaginal wall. This layer gains structural stability through its lateral attachment to the arcus tendineus fascia pelvis and levator ani muscle. The stability of the suburethral layer depends on the intact connection of the vaginal wall and endopelvic fascia to the arcus tendineus fasciae pelvis and levator ani muscles".[257]

This intimate relationship between the anterior vaginal wall and the entire muscular support of the pelvis explains the common finding of pelvic floor tension myalgias resultant to the implantation of noxious materials into or through the anterior vaginal wall. Any chronic inflammation and resultant fibrosis of the anterior vaginal wall directly effects the levator muscles and obturator muscles. Once spasm in any pelvic muscle is elicited, the domino effect begins and pelvic floor tension myalgia results. This effect is not unlike what one would experience if they held the tip of a metal rod over a fire. In moments, one's hand would be burning as the heat traveled down the rod. This phenomenon is one that I have found in women implanted with the TVT-SECUR device and other foreign bodies into the anterior vaginal wall. Pelvic Myofascial Pain syndromes are associated with pelvic floor hypertonicity, hyperalgesia and or allodynia, pelvic pain, dyspareunia, and are often associated with bowel and or bladder dysfunction.

[257] DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. Am J Obstet Gynecol. 1994;170:1713–1723



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It is also important to note that the noxious effects of polypropylene mesh on the muscles of the pelvis often cause extrapelvic pain syndromes. Pelvic nerves including the levator ani nerve, inferior rectal nerve, and pudendal nerve, nerves affected by contracting and inflamed pelvic mesh and resultant pelvic spasm, converge upon the same sacral nerve roots as the sciatic nerve. Consistent with this, the FDA has recently identified an up to 39% incidence of transvaginal mesh related nerve damage with leg pain, thigh pain, buttock pain, and other neurological symptoms.[259] Hence, it is not uncommon for patients with mesh related pelvic floor tension myalgia to have sciatic type symptoms. The converse is however not true. Women with sciatica and without mesh in the vagina, do not develop symptoms of pelvic myofascial pain syndrome.

[258] Modified from Doshani A, Teo REC, Mayne CJ, Tincello DG. Uterine prolapse. *BMJ : British Medical Journal*. 2007;335(7624):819-823. doi:10.1136/bmj.39356.604074.BE.
[259] FDA. Reclassification of Surgical Mesh Instrumentation. Gastroenterology-Urology Medical Devices Advisory Committee Panel. February 26, 2016.

Ethicon taught similar trajectories for its TVT-S hammock method and its TVT-O method. Many patients would suffer recurrent incontinence secondary to the defective TVT-S device. Some of these women have undergone subsequent TVT-O implantations. Additionally, Ethicon taught surgeons that they may put a second TVT-SECUR in a patient who failed the first TVT-SECUR. Women undergoing either a repeat TVT-SECUR procedure or TVT-SECUR and TVT-O procedures have two layers of the defective PROLENE in the same tract. This is a method that increased the mesh load, foreign body load, per unit area of body tissue. As noted elsewhere herein, the foreign body reaction associated with polypropylene mesh is directly responsible for many complications by means of acute and chronic inflammation, fibrosis, and contraction. This unique method of increasing the mesh load represents a novel method, a method not encouraged by other purveyors of transvaginal mesh devices.

Whereas the inventor of the transobturator method, Delorme, taught a method to decrease the risk of obturator neurovascular complications, Ethicon opted to ignore such teachings. Delorme taught, "The patient is put in the lithotomy position in hyperflexion, with her thighs bent back on the abdomen at an angle of 120 degrees."

It is known that the T.O.T. method causes large trocars to course as close to the obturator nerve and blood vessels. Whereas Ethicon's Worldwide Director of Medical Affairs, Piet Hinoul, has shown that hip flexion greater than 100 degrees is protective in that it provides an 1.9 cm of separation between trocars and the obturator neurovascular bundle, Hinoul et al have been shown that hip flexion of less than 80 degrees decreases this

distance dramatically to as little as 5mm.[260] The distance from the anterior and posterior branches of the obturator neurovascular bundle is likely much less. As the TVT-SECUR sling diameter is 1.1 cm, there is a high risk of the defective Prolene being in direct contact with vital nerves and blood vessels.[261] Ethicon's TVT-SECUR expert witness, Dr. Brian Flynn, notes in his expert opinion that nerve pain occurs "*as a result of nerve entrapment or irritation*" that "*can occur if the mesh is placed too close to a nerve*".[262] Ethicon opted not to provide the safety teachings of the transobturator inventor and, ignoring the published findings of their own medical director, marketed its novel TVT-S method, a method more likely to cause neurovascular injury.

Numerous other authors, including the inventor of the TVM procedure, Jacquetin, have found a significantly higher incidence of de novo dyspareunia associated with transvaginal mesh surgery. As discussed elsewhere herin, the TVT-SECUR device is associated with ah higher incidence of de novo dyspareunia than other midurethral slings. However, perhaps even more concerning, is that pain syndromes associated with transvaginal mesh, unlike native tissue surgery, are unlikely to resolve with either conservative or surgical intervention. Rogo-Gupta et al recently reported that they were unable to get the majority of their patient with mesh related pain back to a satisfactory quality of life. Thirty-nine percent of patients presenting with pain remained in the terrible to unhappy range of QOL following excision by these experts.[263]

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[260] Hinoul, Piet, Linda Vanormelingen, Jan-Paul Roovers, Eric De Jonge, and StÃ©fan Smajda. "Anatomical Variability in the Trajectory of the Inside-out Transobturator Vaginal Tape Technique (TVT-O)." *International Urogynecology Journal* 18.10 (2007): 1201-206.

[261] Hinoul, Piet, Linda Vanormelingen, Jan-Paul Roovers, Eric De Jonge, and StÃ©fan Smajda. "Anatomical Variability in the Trajectory of the Inside-out Transobturator Vaginal Tape Technique (TVT-O)." *International Urogynecology Journal* 18.10 (2007): 1201-206.

[262] TVT-SECUR expert opinion of Dr. Brian Flynn, wave 3 pg 45

[263] Rogo-Gupta, L., Grisales, T, Huynh, L, Rodriquez, L, Raz, S., Symptom Improvement After Prolapse and Incontinence Graft Removal in a Case Series of 306 Patients. Female Pelvic Med Reconstr Surg 2015;21: 319–324 .

The Learning Curve

Most new procedures are associated with a learning curve. If the learning curve is increased, special measures must be taken to ensure patient safety and acceptable patient outcomes. An example of such special measure would be hands-on proctoring by an expert surgeon until proficiency is ensured. These extra steps may be justified if the given procedure offers substantial benefits over existing procedures. Although Ethicon internal documents suggest that the TVT-S Secur was associated with a longer than typical learning curve, no such special measures were taken to ensure patient safety and optimize outcomes. Furthermore, Ethicon Direct of Medical Affairs, Piet Hinoul, noted in his 2011 published manuscript, that the TVT-S device was inferior to the TVT-O device and failed to demonstrate lower morbidity.[264] In a presentation to the Worldwide Marketing Team in 2007, Marketing Manager Harel Gadot provided that the learning curve was much longer than anticipated (20 cases) and that the surgeon must be dedicated and "live through it". There was no mention about safeguarding the patients.[265]

Ethicon's claims of high failure rates and complication rates attributable to a long learning club are of questionable merit. As noted in the review of the literature cited elsewhere in this monograph, some of the most experienced sling surgeons in the country were unable to achieve acceptable cure and complication rates, even after they had performed over 100 TVT-S implantations. By way of example, in 2008 Neuman published his experience on fifty patients treated with the IFU method of the TVT-

[264] Hinoul, Piet, Harry A.m. Vervest, Jan Den Boon, Pieter L. Venema, Marielle M. Lakeman, Alfredo L. Milani, and Jan-Paul W.r. Roovers. "A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence." *The Journal of Urology* 185.4 (2011): 1356-362.
[265] ETH.MESH.02105223

SECUR device and fifty treated with his modification.[266] Neuman had extensive TVT experience by February of 2008, having performed over 400 TVT-Secur procedures. Neuman, utilizing the method described in the TVT-S IFU noted a 20% failure rate at one month and a 64% overall complication rate. He noted a 10% TVT-S erosion rate and an 8% incidence of button holing. In 2013 Tommaselli et al reported their prospective findings.[267] All surgeons had performed a minimum of 40 TVT-S procedures prior to the study. Utilizing a last observation carried forward analysis, the TVT-S procedure was associated with a 68% objective cure rate.

Ethicon's Worldwide Director of Medical Affairs informed, Axel Arnaud, informed the TVT-S project Lead, David Smith, and Worldwide Medical Director, David Robinson,

> *"The reality of the field is that some surgeons, including KOL's who have been correctly trained and who have passed the learning phase, are raising concerns about the efficacy of TVT Secur. They have hard time to achieve consistently good results with the device.*

Summary Opinion on The Learning Curve

I state with a reasonable degree of medical and medical device industry certainty that Ethicon believed that the low efficacy and high complication rates of its TVT-SECUR device were, in part, secondary to a unique learning curve yet provided no

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[266] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

[267] Tommaselli, Giovanni A., Alessandro Dâ™Afiero, Costantino Di Carlo, Carmen Formisano, Annamaria Fabozzi, and Carmine Nappi. "Tension-Free Vaginal Tape-O and -Secur for the Treatment of Stress Urinary Incontinence: A Thirty-SixMonth Follow-Up Single-Blind, Double-Arm, Randomized Study." *Journal of Minimally Invasive Gynecology* 20.2 (2013): 198-204

remedy that would protect the women of the world from resultant harm. I state with a reasonable degree of certainty that the material and method defects of the TVT-SECUR device were responsible for any such prolonged learning curve and that such defects were sufficiently severe that even expert surgeons would not overcome such learning curve, and therefore such learning curve was defective and caused harm to women. I state with a reasonable degree of certainty that, to the extent that efficacy substantially improved and complications substantially decreased with completion of the "learning curve", the remaining material and design defects were sufficiently severe that efficacy would remain low and complications would remain high.

Summary Opinion of Method and IFU

I state with a reasonable degree of medical certainty that the TVT-S method and label were defective, Ethicon was aware of these defects, Ethicon refused to update its IFU even though it believed that the IFU needed to be precisely followed. To the extent that the learning cure may have been prolonged, as postulated by Ethicon, I state with a reasonable degree of medical certainty that Ethicon failed to provide the necessary training to protect patients during this "learning curve" and that the experimental TVT-SECUR device did not offer any substantial benefits that would justify either such training or the risks to women associated with such training.

The TVT-SECUR IFU Was Defective[268]

Product Description

> *"PROLENE polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE polypropylene nonabsorbable surgical suture. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE mesh is knitted by a process that interlinks each fiber*

[268] ETH.MESH.02340568

junction and which provides for elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body".

Both the scientific and medical literature (including Ethicon's own investigations) have consistently shown that PROLENE polypropylene is reactive. Indeed, Ethicon's animal studies demonstrated that the material is reactive, creating chronic inflammation and destroying tissue. Ethicon Worldwide Director of Medical Affairs, Piet Hinoul, has taught that meshes are not biologically inert.[269] Although Ethicon realized the importance of mesh elasticity, there is almost a complete loss of elasticity after implantation and it created a novel mesh that was extra stiff (by way of laser cutting). Ethicon's label herein misleads the user to believe its sling is uniquely inert and elastic.

"The resultant fleece material is of sufficient pore size to allow continuing growth of cells and intrinsic body tissue. The sandwiched fleece ends are mainly undyed, soft, expandable, and pliable". "Absorption of sandwiched fleece ends is essentially complete within approximately 90 days. The fleece layers are replaced as connective tissue grows into the mesh". "Animal studies show that implantation of PROLENE mesh and the absorbable fleece sandwich material made from VICRYL and PDS yarn elicit a minimal inflammatory reaction in tissues, which is transient and is followed by the deposition of a thin fibrous layer of tissue, that can grow through the interstices of the mesh system as the fleece portion is being absorbed, thus incorporating the mesh into adjacent tissue. The PROLENE material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes".

This statement is not only unsupported in clinical trials or other high level evidence, Ethicon had previously reported to the FDA that its fleece was an "impermeable sheet of material" not allowing ingrowth but, rather, only allowing "on-growth". Furthermore, this microporous "fleece" had neither been approved nor cleared for vaginal implantation and I am unable to find any documentation to support that the

[269] ETH.MESH.01264260 (Presentation, "Prolift+M," P Hinoul, MD, Ethicon Pelvic Floor Expert's Meeting – Nederland, Utrecht, May 7, 2009).

novel heat welded ETHISORB Dura Patch elicits only mild and transient inflammation.[270] As noted elsewhere herein, PROLENE degrades. Ethicon herein misleads the surgeon to believe its novel fleece material fosters ingrowth and its mesh does not degrade.

General Preparation

> *"Place the patient in the lithotomy position; maintain the table and patient parallel to the floor".*

As noted elsewhere herein, Ethicon's own medical director had published his finding on the importance of hip flexion greater than eighty degrees. This position would decrease the risk of nerve injury and was consistent with the teaching of the inventor of the transobturator procedure. Ethicon opted to omit such vital teaching from its label.

> *"After initiating sharp dissection, continue with a small pair of blunt scissors, making two small paraurethral dissections (approximately 1.0 cm. NOTE - These dissections can be made directionally aligned with the surgeon's choice of either the "U" (at 45° from the sagittal midline) or "Hammock" (9 and 3 o'clock positions or parallel to the floor)"*

This teaching suggests that the Hammock and "U" methods have equal safety and efficacy. However, Ethicon had not evaluated such prior to market launch and failed to inform of this unknown. As noted elsewhere in this monograph, it would later be shown that the two methods were not equally efficacious. The label was not updated.

> *"To minimize the chance of damage to organs, vessels, or other anatomic structures, keep the tip of the Device in close contact with the inferior-posterior aspect of the pubic bone as you insert the Device into the connective tissue of the urogenital diaphragm. NOTE- When the Device is firmly in the connective tissue - STOP. NOTE - As a guide, you may use the markings on the Inserter to aid in this initial positioning.*

[270] K991413

This is an ambiguous teaching that encourages harm. A surgeon cannot determine "firmly" and does not know how to use the markings. Ethicon does not teach how to use the markings. Hence, a surgeon is encouraged to push the device until he or she perceives an undefined sensation of firmness. This increases the risk of injury.

> *"NOTE Adjustment of the Device to achieve tension-free placement should be made by moving the Inserters- NOT by pulling on the mesh" and "Assess the positioning of the tension-free tape, (i.e., cough test or other means). NOTE - The final position of the Inserters should be similar, but they do not need to be symmetrical as shown in FIGURE 7".*

Ethicon neither teaches a reproducible means of "tension free placement" nor defines tension-free. Furthermore, Ethicon does not teach "other means" of positioning and, implicit therein, is a teaching ad-lib surgery. As discussed elsewhere in this monograph, Ethicon later realized that the label failed to adequately teach tension. The label was never updated.

*(Hammock position)"*When the *Device* is firmly in the (obturator) internus muscle - STOP. NOTE - You may use the markings on the distal end of the *Inserter* to aid in this initial positioning".

As noted elsewhere herein, Ethicon was well aware of the risks associated with obturator nerve injury. Ethicon's Medical Director, Piet Hinoul, had previously published on the importance of hip flexion when performing an "in to out" obturator penetration. Flexion of less the eighty degrees was shown to bring the needles within 5 mm of the obturator nerve. The TVT-S mesh was wider 11 millimeters wide. The inventor of the obturator method of sling surgery had previously described the importance of hip flexion. Rather than provide the safety teachings of Delorme, findings validated by Ethicon's own

medical director, Ethicon opted to omit such teachings. This teaching toward nerve injury was compounded by the ambiguous teachings of depth of insertion.

Warnings and Precautions.

> *"The patient should be instructed to contact the surgeon immediately if dysuria, bleeding, or other problems occur".*

Ethicon neither described nor defined other problems. Ethicon did not warn of the signs and symptoms of mesh erosion such as those of dysbiosis, recurrent UTIs, or dyspareunia. Ethicon did not warn of signs of voiding dysfunction from overcorrection.

> *"As with other incontinence procedures, de novo detrusor instability may occur following a sub-urethral sling procedure utilizing the GYNECARE TVT SECUR System. To minimize this risk, make sure to place the tape as described above"*

Ethicon misleads the user to believe that risks can be minimized if the user follows the ambiguous and dangerous instructions. One cannot control mesh contraction, inflammation, and contamination related infection. Furthermore, Ethicon herein misleads the user to believe the risk of de novo instability is similar to that of other incontinence procedure. Ethicon performed no clinical trials capable of assessing such prior to market launch. Later studies would demonstrate that the TVT-SECUR was indeed associated with a higher incidence of detrusor instability symptoms than other slings.

Ethicon's TVT-SECUR expert witness and preceptor, Dr. Brian Flynn has stated that TVT may not be appropriate half of his patients and states "*I use biological graft material in 50% of cases*". Dr. Flynn offers examples of such patients including those who have failed a previous surgery, those with neurogenic dysfunction, and those with fistula).[271]

[271] TVT-SECUR expert opinion of Dr. Brian Flynn pg 33

The warnings against use of the TVT-SECUR product in various patient populations such as those taught in the expert opinion of Dr. Flynn are conspicuously absent from the IFU. Even more concerning is that Ethicon's internal documents demonstrate that it advocated the use of its TVT-SECUR in those who had failed previous surgery.[272] Although Dr. Flynn suggests that his situation is unique, as he works in a tertiary care center with complex patients, with a TVT-SECUR failure rate in excess of 20%, the treatment of surgical failures would be common in the general community. Furthermore, experts operating in referral centers should also have been warned.

Adverse Reactions

> *"Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation or inflammation".*

As noted elsewhere herein, polypropylene mesh is associated with a chronic foreign body reaction. Ethicon's PROLENE was no exception to this rule. Ethicon's own studies had demonstrated chronic inflammation. This claim misleads the user to believe that Ethicon's polypropylene mesh was unique and did not cause a chronic inflammation and foreign body reaction.[273]

Missing

Absent from the– label are all warnings of acute and chronic groin pain, leg pain, dyspareunia, recurrent urinary tract infections, chronic erosion, vaginal dysbiosis, the

[272] ETH.MESH.03179016
[273] See also ETH.MESH.04093125 (Dr. Meng Chen, Assoc. Medical Dir. WW Customer Quality at Ethicon responded "Pardon me again, from what I see each day, these patient experiences are not 'transitory' at all.")

signs and symptoms of such adverse events, and instruction for managing such adverse reactions specific to the TVT-SECUR defective material and method. Absent from the label is a warning of the risk of inability to remove the device in its entirety. Also absent from the label is a discussion of uncertainties and differing opinions. Including in the missing information is that the entirety of human safety and efficacy data at time of product launch was limited to only five weeks of data in small group of women treated by expert TVT surgeons and that the safety and efficacy of the TVT-SECUR device had not yet been established. Indeed, Ethicon could not qualify or quantify risks of pain, erosion, infection, dyspareunia, or failure. It had no meaningful data on such. This was not disclosed. Although it would later be determined that efficacy was lower than that of other slings and the risks of erosion, urge symptoms, and dyspareunia were higher, the label was never updated.

The IFU Label Was Not Validated

In order to be effective, an IFU must allow the user of a device to use a device safely and effectively for its intended purpose. The industry standard is to validate the label in a Design Validation Lab. As noted in my chapter on Design Validation, Ethicon biased the validation of its IFU by providing the surgeons with additional information. Prior to evaluation of the product, study participants were "trained by appropriate ETHICON representative", "saw and reviewed the Big Print of the Procedural Steps Guide Line", saw and reviewed a video of the procedure, and read the IFU. If the surgeons were able to safely and effectively perform the procedure, the IFU would not have been validated as the IFU is not packaged with a training video, a Big Print

Procedural Steps Guideline, and an Ethicon representative. However, even this constellation of labels did not prove to be sufficient to allow effective use of the product.

The Patient Labels Were Defective

The TVT Product Line Patient Brochure was Defective

Ethicon provides patient brochures to physicians. Physicians routinely use these brochures to inform their patients of the risks, benefits, and alternatives. Ethicon TVT-SECUR expert Jaimie Sepulveda has opined *"These instruments (patient brochures) have been used and continue to be used by trained pelvic surgeons as a standard of practice in the counseling of their patients*".[274] The effects of a defective label are apparent.

This TVT Patient brochure promotes the TVT product line including TVT, TVT-O and TVT-S devices[275]

> *"The only procedure of its type with 7 years of proven results - clinically proven, safe and effective"* [276]

This is an ambiguous and misleading statement. This statement would, more likely than not, cause a lay person to believe that this is the TVT procedures (including the TVT-S) are the only incontinence procedures with seven years of proven results. This statement is false.

- There were decades of results that had proven traditional autologous slings and retropubic urethropexies safe and effective.
- Ethicon herein is citing a seven-year prospective evaluation of its full length TVT

[274] TVT-SECUR expert report of Dr. Jaimie Sepulveda, wave 3. Pg 23
[275] ETH.MESH.08003263-78
[276] ETH.MESH.08003263-78

sling.[277] Hence, any claims of safety and efficacy do not apply to its novel, experimental TVT-SECUR product. Ethicon's own Women's Health and Urology World Wide Marketing Director had noted in an email to the TVT-SECUR Project Lead, "TVT SECUR is a new product/techinique and therefore there is little relationship to the 7-year database (TVT mechanical cut data) other then it is the same PROLENE mesh".[278]

- Ethicon herein is citing a seven-year prospective evaluation of its full length TVT sling, a study without a control group, that implanted the sling under local anesthesia (a method only rarely used by U.S. surgeons)
- Ethicon herein is citing a seven-year prospective evaluation of its full-length TVT sling, a study without a control group, that did not track complications such as pain or dyspareunia.
- Ethicon herein is citing a seven-year prospective evaluation of its full length TVT sling and does not disclose that only seventy percent of its subjects returned for examination.

This ambiguous and misleading marketing message is conspicuously missing from the subsequent 2015 TVT product line brochure.[279] This ambiguous and misleading marketing message had been replaced by a new misleading marketing message, "*GYNECARE TVT is supported by over 17 years of clinical data -- more than any other sling on the market. This "17 year data*" is a the continuation of the 7 year observational

[277] Nilsson, Carl Gustaf, Christian Falconer, and Masoumeh Rezapour. "Seven-Year Follow-up of the Tension-Free Vaginal Tape Procedure for Treatment of Urinary Incontinence." *Obstetrics & Gynecology* 104.6 (2004): 1259-262.

[278] ETH.MESH.00858252

[279] Gynecare TVT "Stop coping. Start Living. What you should know about stress urinary incontinence". http://www.ethicon.com/sites/default/files/managed-documents/031295-150316_tvt_patient_brochure11_cr_0.pdf

study previously referenced, an observational study with not control group. The word "support" is ambiguous and suggests that there is 17 years of data that supports the entire TVT product line. As noted above, this data does not relate to the TVT-SECUR device.

> *"GYNECARE TVT is the only treatment of its type with the longest-term clinical results. It's clinically proven, safe and effective*"[280]

This statement is misleading and inaccurately causes the reader to believe that the TVT is the only midurethral sling available and that there are no sling surgeries with longer-term clinical results.

- As already noted herein, the GYNECARE TVT did not have the longest-term clinical results. Traditional slings had decades more of clinical results. Although a gynecologist or urologist could interpret this to be a claim referencing only synthetic midurethral slings, a layperson would not be expected to make this interpretation. This statement also misrepresents GYNECARE TVT to bet the "only treatment of its type". Even if a layperson was to interpret this as a claim related to midurethral synthetic slings, there were many alternative commercially available slings at the time.

Not only did Ethicon mislead women to believe that its TVT-SECUR product had been proven safe and effective and that its TVT products were the only sling procedures with seven years of safety and efficacy data, they based this misleading claim on a study that did not demonstrate safety. Ethicon removed this misleading marketing message from its 2015 TVT product line patient brochure.

> *"98% of women treated with GYNECARE TVT are still dry or report*

[280] ETH.MESH.08003263-78

significantly less leakage 7 years after treatment"[281]

This is a misleading statement that caused women to believe failure rate of all TVT products was lower than actual failure rates.

- This statement was a misrepresentation of the data and misleads women to believe that there would be only a two percent chance of failure. The study cited by Ethicon did not find "98% of women treated with TVT to be dry or with significantly less leakage, the study demonstrated 87% to be subjectively cured or improved (ten patients were lost to follow-up). If Ethicon had provided the correct information from the referenced study, a women reading the brochure would, more likely than not, have believed that she would have a 13% rather than a 2% risk of failure. However, even this information would be misleading, as it would not apply to the TVT-SECUR product, a product with double the failure rate of full-length slings.

- Additionally, the findings of the referenced study could only be extrapolated to the full length TVT device performed under local anesthesia, a method only rarely used in the United States.

  In 2011 and beyond, Ethicon continued to cite this same study group.

  > *"Moreover, 97% of women surveyed following treatment with GYNECARE TVT" were still dry or had significantly less leakage 11 years later! These women were so satisfied with the treatment that 97% said they would recommend the procedure with GYNECARE TVT' to a friend".*[282]

- Ethicon here continues to cherry-pick quotes from a full length TVT retropubic

[281] ETH.MESH.08003263-78
[282] ETH.MESH.08003291

manuscript that serves to mislead the reader. The same sentence of the same manuscript reports that 77% of women regarded themselves as cured. Ethicon omitted this portion of the sentence. Ethicon also opted not to note that 23% of the women were missing from the data set. A correct and not misleading statement is "A recent evaluation of women who were available for follow-up found that 77% considered themselves cured". Even this statement would be somewhat misleading as it does not offer the range of cure that would include those lost to follow-up. By way of example, allowing missing data to be failure, only 59% of women would consider themselves cured. The above noted narrative from Ethicon also continues to mislead the reader to believe that this result applies to the TVT Product line. As noted above, it only applies to the full length TVT device performed under local anesthesia, a method only rarely used in the United States. As note elsewhere in this monograph, Ethicon new this data did not apply to its TVT-SECUR device. Perhaps even more shocking is that an Ethicon physician marketing brochure-advertisement provides this quote"

"You can not transfer results from one procedure with certain design and material to another one that looks alike, but has some differences"[283]

Ethicon removed this misleading marketing message from its 2015 TVT product line patient brochure.

> *"Used to treat over 1 million women worldwide, more than any other procedure of its type "*

This is a misleading statement that, more likely than not, would cause a woman to believe that TVT-SECUR been used on over one million worldwide. This was certainly

[283] ETH.MESH.01186070

not true at the time of publication of this document.

Ethicon removed this misleading marketing message from its 2015 TVT product line patient brochure.

> *"Few patients experience complications" and "The rate of complications with GYNECARE TVT is very low".* [284]

This is both an ambiguous and inaccurate statement that misleads the reader to believe that complications rates of the TVT product line were less than the actual rates.[285]

- At the time of this publication, numerous studies had reported complication rates. "Few" and "very low" are ambiguous descriptions.
- The rate TVT-SECUR related dyspareunia has been shown to be as high as 8% and has been shown to significantly higher than that of other midurethral slings.
- The rate of TVT-SECUR erosion was shown by Hinoul to be as high as 29% and was demonstrated to be significantly greater than other midurethral slings.
- The rate de novo urgency associated with the TVT-SECUR was shown to be more than double that associated with the TVT retropubic device.
- The rate of hemorrhage was found to be greater with the TVT-SECUR device.

Ethicon removed this misleading marketing message from its 2015 TVT product line patient brochure.

Risks 2008

> *"All medical procedures present risks. As with all procedures of its type, there's a risk of injury to the bladder and surrounding organs. For a complete description of risks, see the attached product information".* [286]

The attached information is represented by a portion of the defective IFU

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[284] ETH.MESH.08003263-78
[285] The high complication rates are described in more detail elsewhere herein as well as within the most heavily weighted studies of the 2015 Cochrane meta analysis.
[286] ETH.MESH.08003263-78

narrative. The attached information does not provide a "complete description of the risks". It fails to disclose the risks of pain with intercourse, chronic pain with intercourse, untreatable pain with intercourse, pelvic pain, chronic pelvic pain, untreatable pelvic pain, tension myalgia, myofascial pain syndrome, vaginal dysbiosis, vaginitis, recurrent urinary tract infections, erosion, and the inability to remove the device. The attached information misleads the reader to believe that failure of the procedure and urinary obstruction are results of surgical technique and not the defects of the device, *"Improper placement of the TVT device may result in incomplete or no relief from urinary incontinence or may cause urinary tract obstruction".*

It should be noted that a later brochure, one printed at least four years later, changed this language from the above, *"All medical procedures present risks. As with all procedures.."* to *"All surgical procedures present some risks. Complications associated with sling procedures with synthetic mesh include…".*[287] Ethicon herein appears to have been motivated to be less misleading and had taken a moderately corrective action. Although this same brochure also adds many risks missing from the warnings of the earlier brochure, it opts not to disclose that many complications may result in permanent symptoms. Additionally, this same brochure teaches women that the foreign body reaction will be transient and that such transient reaction could result in erosion or fistula formation.

> *"Transitory local irritation at the wound site and a transitory foreign body response may occur. This could result in extrusion, erosion, fistula formation or irritation"*

Ethicon has provided the patient with false information, Ethicon knew the reaction was not transitory. By coupling the complications to a transitory response,

[287] ETH.MESH.08003301

Ethicon misleads women to believe the risks of those complications are transitory.

The 2015 updated TVT Product Line Brochure

In addition to the retracted misleading marketing messages noted above, the 2015 brochure provides a new set of misleading marketing messages.

> "*After further review of the clinical studies for SUI, an FDA Panel concluded that the retropubic and obturator slings currently on the market have been extensively studied, and the safety and effectiveness of these devices is well-established"*.

This is not what the FDA had published. The FDA indicated that it found safety and effectiveness at one year. The layperson would not be expected to understand that even the correct version of the FDA statement did not pertain to the experimental TVT-SECUR sling.

> *"The body then naturally incorporates the mesh into the surrounding tissue, preventing future leakage*".

The 2015 patient brochure misrepresents the PROLENE mesh. As described in detail elsewhere herein, the defective PROLENE mesh creates a chronic foreign body reaction and becomes captured inside a bridging fibrosis. Ethicon misleads women to believe that its slings are not associated with a rejection type process.

"*You may have minimal scarring and should not feel the mesh once it has been placed*"

This is a gross misrepresentation of the facts. As noted elsewhere herein, the incidence of TVT-SECUR mesh erosion was found to be 4 times greater than that of other midurethral slings, occurring in up to 29% of cases.

Risks 2015

> "*Risks Common to All Pelvic Surgeries"*

This is a new section, a section not included in previous patient brochures. Although

this section provides warnings of chronic pain with intercourse, chronic pain, chronic pelvic pain, nerve damage, and chronic neuro-muscular problems, it misleads women to believe that these risks are common to pelvic surgeries and that the risks associated with TVT are the same as those associated with other surgeries.

- "Common" is an ambiguous term and ambiguous language creates a defective label. However, more importantly, the above noted chronic complications are not commonly associated with all pelvic surgeries.
- These complications, when associated with native tissue surgeries are almost always transient or treatable. However, these complication, which are common with mesh implantation, are often chronic and untreatable.

This misleading statement causes the reader to believe, incorrectly, that the described risks are no less likely to occur if they chose an option other than TVT-SECUR.

Other embodiments of the TVT Product line patient brochure offered additional misleading statements.

> "*Your surgeon will place a think piece of soft, flexible mesh through tiny incisions in the abdomen and vaginal to support the urethra".*[288]

As noted in the material defects chapter of this monograph, the PROLENE mesh becomes hard and brittle after implantation. This patient brochure was printed in or after 2011 (copyright mark). By this time the problems of vaginal mesh encapsulation, contraction, and loss of elasticity and complications resultant to such were increasingly described in the medical literature. Ethicon here misleads the patient to believe that they will have a soft and flexible piece of material placed into their vagina, an area that absolutely must remain soft and flexible to preserve a woman's ability to have

[288] ETH.MESH .08003300

intercourse with her partner. To unlikely extent that the patient was aware of the defects of transvaginal polypropylene mesh, Ethicon herein misleads them to believe that the TVT mesh is unique and they will have a soft, flexible implant in their body. The correct statement, "the TVT mesh, once implanted, is expected to become encapsulated with loss of flexibility" was omitted and the patient mislead away from the truth. Additionally, Ethicon product IFUs taught incision size. However, Ethicon opted to use the ambiguous description, "tiny". Industry related label guidance including that from the FDA discourages the use of both ambiguous and misleading language.

The Physician Labels Were Defective

Brochures and Other Printed Media

A physician – surgical center type advertisement-marketing piece, published some time in or after 2008 mislead physicians

"94% objective success rate" (TVT-SECUR)[289]

Ethicon misleads the physician to believe that the 94% objective success had been demonstrated at one year. This indicates that the TVT-SECUR is likely to be the most effective sling in the world. As we now know, it was perhaps one of the least effective. This study referenced cited by Ethicon was a prospective observational study by one of the world's most experienced TVT-SECUR surgeons. He was unable to achieve the referenced success with the TVT-SECUR method. achieved this result by modifying the method, this method was never validated by subsequent randomized clinical trails, this method resulted in a high rate of dyspareunia and resultant resurgery, resulted in a high

[289] ETH.MESH.01186071

rate of urge symptoms, and this modification was never added to the IFU. Furthermore, objective success was not actually demonstrated. This success was measured by a phone call to the patient.

"...greater mesh slip force for immediate secure implantation"[290]

This misleading information appears immediately after the "94% objective success rate" narrative and adds misleading information that would provide false credibility to that statement. As noted elsewhere herein, the TVT SECUR was not secure. One of the greatest problems faced by Ethicon was the dislodgement of the sling during the implantation process. Furthermore, Ethicon had not tested the pull-out force of the TVT-SECUR in a living animal. This living animal pull-out data was based on a barbed fixation end Ethicon did not market. As this document references an internal document, Ethicon may have obtained bench data comparing TVT-SECUR pull out to MiniArc pull out. Indeed, an adjacent table suggests that this "mesh slip force" data was obtained in a glass dish. This could in no way validate in vivo "immediate secure implantation".

This same document touts *"minimal" blood loss.* However, as noted elsewhere herein, by 2008 there was already a growing pool of evidence demonstrating increased blood loss associated with the TVT-SECUR device. This would later be validated by the systematic reviews of the literature.

Another TVT-SECUR Physician brochure misleads surgeons.[291]

"Less complicated procedure" "GYNECARE TVT SECUR system is designed to reduce the number of procedural steps"

This misleads the surgeon to believe that the TVT-SECUR procedure is less

[290] ETH.MESH.01186071
[291] ETH.MESH.05795097

complicated to perform than other sling procedures. However, the TVT-SECUR was more complicated procedure with more procedural steps than any other midurethеral sling. Ethicon's TVT retropubic IFU provided a single page of procedural instructions with ten or less procedural steps. Ethicon's TVT-SECUR IFU provided eight pages of difficult to interpret instructions with 23 procedural steps. As noted elsewhere herein, the procedure was so complicated that Ethicon built a "cookbook" to assist surgeons and even the most experience TVT surgeons had trouble with the procedure. The Ethicon professional education slide deck utilized by TVT-SECUR instructor Dr. Jaime Sepulveda dedicated 16 slides to teaching the removal of the TVT-SECUR inserter.

Ethicon's Australian Medical Director, Aran Maree, noted in October of 2007, "I know that the Australian regulator, with whom I regularly discuss our adverse events, may well suggest that this device may be more successful on the drawing board than in reality because the average practitioner finds it too complicated to insert correctly or cannot master the process. In this case, if some surgeons cannot achieve competency early on, we should restrict access to those who can"[292].

> *"Absorbable Fixation Tips-provide mechanical fixation until complete tissue ingrowth can occur"*.

This provides non-factual and misleading information. My review of the internal documents and medical literature demonstrates no evidence to support this statement. Ethicon's opted not to perform any in vivo studies on the fixation of the its experimental Dura Patch fixation tips. Both the high immediate failure rate and short-term recurrence rate described elsewhere herein are evidence in direct contradiction to "fixation until complete tissue ingrowth occurs". The Rezapour micrographs found elsewhere in this

[292] ETH.MESH.00642327

monograph provide no support to Ethicon's claim. This misleading claim of Ethicon, more likely than not, causes the reader to believe that TVT-SECUR fixation tips are not defective.

Ethicon continues to further mislead on the fixation of its experimental TVT-SECUR device:

> *"In animal studies, tissue ingrowth into the mesh implant was complete prior to Fixation Tip absorption"*
> *"The strength of fixation of the mesh implant at the time of the procedure, as well as during the initial stages of tissue ingrowth, is equivalent to or greater than the reliable fixation of GYNECARE TVT - Mean initial pullout force was 864 g for the GYNECARE TVT SECUR System cared with 771 g for the GYNECARE TVT"*

Ethicon herein is misrepresenting the findings of the three month live sheep study of Rezapour et al. As discussed in the review of the medical literature section of this monograph, the fixation-tip absorption micrograph taken at 12 weeks does not shows very little tissue integration. Although Ethicon is most likely correct and tissue integration is complete (as good as it is going to get), there is minimal to no tissue integration between the mesh fibers. Ethicon uses word-smithing to suggest that there is a full tissue ingrowth. However, there is almost none. Even more misleading is Ethicon's statement with regard to fixation strength. First and foremost, the referenced data does not apply to the TVT-SECUR device. The pull out strength data of Rezapour et al pertains only to the barbed anchor of the tested TVTx device. Rezapour et al did not study the TVT-SECUR device. Futhermore, Ethicon misleads the reader to believe that the fixation strength is equivalent to or greater "reliable fixation of the GYENCARE TVT". However, Ethicon does not know if the TVT would provide reliable fixation in a single incision method. In fact, the incorporation of the experimental fixation end onto

the TVTx and TVT-SECUR devices indicates that Ethicon did not believe the GYENCARE TVT would provide reliable fixation. Additionally, the Rezapour study did not evaluate the GYENCARE TVT during the initial stages of tissue ingrowth. In summary, Ethicon's message is "There will be great tissue integration into the ends of the mesh before our great and proven anchor is absorbed, and the resistance to pull-out is just as good as the TVT device you have been using for years". The former was not true. The later was ever tested and, based on the TVT-SECUR failure rate, unlikely to be true.

Ethicon then fails to disclose important uncertainties and misleads the reader to believe the experimental use of Dura Patch in the vagina will be safe.

"RELIABLE

The Absorbable Fixation Tips of the GYNECARE TVT SECUR System are made of VICRYL (polyglactin 91O) suture yarn and PDS (polydioxanone) suture yarn-used as implants for nearly 50 years "

Ethicon does not disclose that this material was never cleared for treatment of stress urinary incontinence and had never been tested for safety when implanted in the human vagina.

Ethicon then continues by providing by providing misleading data on a different product and does not notify the reader that such data is not on the TVT-SECUR product being advertised.

"97% success rate"

As discussed in the my chapter covering the patient brochures, this is a misleading statistic from a full-length TVT (not a TVT-SECUR) study and the same sentence of the same manuscript reports that 77% of women regarded themselves as cured. Not only does

Ethicon mislead the reader by slipping TVT data into its TVT-SECUR advertisement, as note elsewhere herein, Ethicon was well aware that such data did not apply to its TVT-SECUR device.

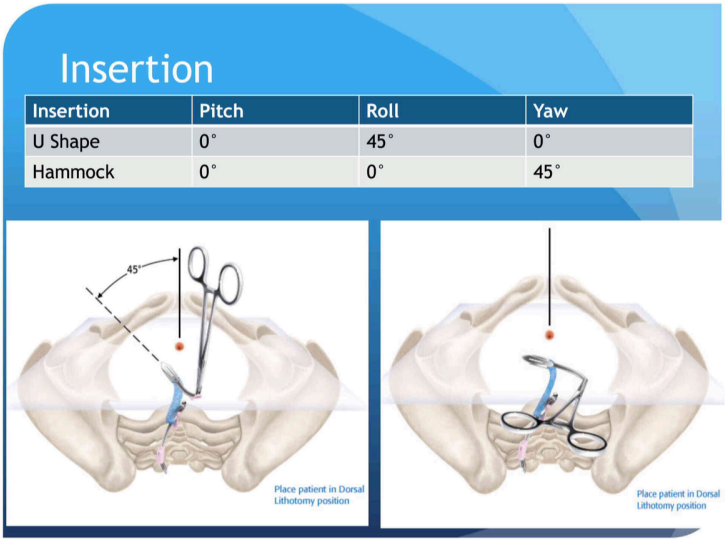
> *"You can not transfer results from one procedure with certain design and material to another one that looks alike, but has some differences"*[293]

Professional Education

The Dr. Jaime Sepulveda Professional Education Presentation[294]

Dr. Supulveda provides a graphical and text teaching of the TVT-SECUR procedure. One such slide is shown below. Dr. Sepulveda here tries to improve upon the difficult to understand "45 degree" instruction of the TVT-SECUR instruction manual. In doing so, Dr. Sepulveda uses descriptive terms most commonly used in the worlds of aviation and boating, "pitch", "yaw" and "roll". I am commercially rated twin pilot an boat captain and have difficulty understanding these instructions. It is unlikely the typical surgeon would understand this description. As noted elsewhere herein, Ethicon's internal documents indicate the surgeons continued to have difficulty with the implantation method.

[293] ETH.MESH.01186070
[294] ETH.MESH.03472421



As noted elsewhere herein, the method of inserter removal was so difficult to understand and perform that an Ethicon TVT-SECUR professional education slide dedicated 16 of 29 procedural slides to removal of the inserter. Only 3 of 29 slides were used to teach insertion of the inserter.[295]

The Dr. Mickey Karram Professional Education Presentation[296]

This Ethicon professional education document teaches the reader that the TVT-SECUR development involved "Hundreds of animal and human caver mesh placements". This misleads the reader to believe that the development process was not rushed and was comprehensive. My review of the internal documents referenced herein suggests that this number is off by as much as 10 X, with the correct number being tens and not hundreds.

This Ethicon professional education document teaches the reader that the TVT-SECUR is *"Less complicated. GYNECARE TVT SECUR System is designed to reduce the*

[295] ETH.03472421
[296] ETH.MESH.00136850

number of procedural steps". As discussed elsewhere herein, the TVT-SECUR would be the most complicated mid-urethral sling with a number of procedural steps many fold greater than other slings.

Consistent with the misleading printed marketing media, This Ethicon professional education document misleads the reader to believe that the TVT-SECUR fixation had been validated in a live sheep study. It does not disclose that the TVTx fixation anchor was a barbed "arrow-head", a fixation technology with hundreds of years of validation, and that the TVT-SECUR fixation anchor had no such barbs (and had not been tested in vivo).

Press Release for Canada[297]

In July of 2008 Worldwide Director of Medical Affairs, David Robinson, prepared a response for the Canadian press. This press release contained inaccurate and misleading information.

> "The device uses the same unique PROLENE polypropylene mesh proven safe and effective with ten years of clinical data". "It has been used in over one million GYNECARE TVT patients worldwide"

This statement is not correct. As noted elsewhere herein, the polypropylene mesh of the TVT-S had different properties than that represented by the ten years of data. The TVT-S mesh had been laser cut, causing changes in pliability. These changes had not been tested in clinical trials.

> "Prior to making GYNECARE TVT SECUR commercially available, we validated the safety of the device in a clinical protocol (humans) in 6 sites in Europe and the U.S.".

[297] ETH.MESH.02113169

As noted elsewhere herein, Ethicon did not validate the safety and efficacy prior to or after launch. The clinical protocol noted by Dr. Robinson provided data only five weeks of data prior to product launch.

The Material Was Defective

The Human Body Has an Adverse Effect on Polypropylene.

The TVT-S implants are made of PROLENE polypropylene mesh. Although it is beyond the scope of this report to teach the microbiology of the human immune system or material science, the basic components of such provide a simple explanation of how and why polypropylene mesh (PPM) implantation is associated with acute and chronic inflammation, oxidation, degradation, scaring, contraction, and loss of elasticity. This is not scientific or medical theory. These are hard medical and scientific facts that have been demonstrated, consistently, in both retrospective and prospective studies.

The Foreign Body Reaction

PPM is a foreign body. It is a attacked by the innate immune system. The attacking cells act to breakdown and digest the foreign body in a process call phagocytosis. When a non-biodegradable foreign body is implanted permanently and is too large to be phagocytized, a process of frustrated phagocytosis occurs. In frustrated phagocytosis, macrophages and foreign body giant cells (hereby referenced as “FBGCs”) release mediators of degradation into zone between the cell membrane and the implanted material surface. PMNs and Macrophages (and FBGCs) , immune cells responsible for this attack, release increasing amounts of the powerful oxidizing agents: ionized oxygen,

hydrogen peroxide, and hypochlorite. Reactive oxygen intermediates can cause surface oxidation with degradation of polypropylene.

One of the world's larger manufacturers of the polypropylene resin, Phillips Sumika, warned that "the material like other polyolefins (the type of plastic used to make polypropylene), can be attacked by some strong mineral acids, halogens, and oxygen. The effect of strong oxidizing agents is an attack on the polymer chain resulting in eventual embrittlement of the resin," and that these molecules can attack the polypropylene resin "causing degradation of the resin."[298] Phillips Sumika warned against the use of their Marlex PPM resin in humans.

Among these chemicals that are known to "attack" this polypropylene and cause the embrittlement and degradation are (1) oxygen, and (2) hydrogen peroxide, and (3) Hypochlorite. The exact chemicals released in the above described reaction of the human body to the implanted PPM. A classical study, known in the art since 1976, demonstrated that the remarkable oxidative changes of implanted PPM. Even though the oxygen concentration in human tissue is substantially less than room air, this study demonstrated that the oxidative changes occurring to implanted PPM were greater than would be expected with exposure to 100% oxygen.[299] This extreme oxidation can only be explained by the well-demonstrated inflammatory response (and associated release of hydrogen peroxide, hypochlorite and reactive oxygen species by inflammatory cells). Numerous studies have since confirmed the oxidative degradation of implanted PPM with resultant contraction and loss of elasticity.[300] A recent study published in the Journal

[298] TSM 308: Chemical Resistance of Marlex Polyproylene. Phillips Sumika
[299] Liebert, Timothy C., Richard P. Chartoff, Stanley L. Cosgrove, and Robert S. Mccuskey. "Subcutaneous Implants of Polypropylene Filaments." .Journal of Biomedical Materials Research J. Biomed. Mater. Res.</i> 10.6 (1976): 939-51.
[300] Fayolle B, Audouin L, Verdu J. Oxidation induced embrittlement in polypropylene - a tensile testing study. Polymer Degradation and Stability. 2000;70(2000):333-40. Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant.

of Material Science not only further validated the in vivo degradation of PPM, but found that such degradation was not evident in other meshes; "The polypropylene mesh demonstrated chemical degradation via oxidation, permanent distortion of the mesh, and changes in thermal properties. While chemical degradation was not conclusively evident in PET and ePTFE...,."[301] Even studies offered by the few remaining advocates of transvaginal PPM implantation demonstrate significant contraction of the PPM with almost complete loss of elasticity.[302] Although the loss of elasticity and contraction is in part secondary to the severe scarring created by the foreign body reaction, studies that have removed the scar have demonstrated that the mesh remains contracted and inelastic.[303]

As noted above, the body's attack on PPM with subsequent degradation is a fact supported by decades of evidence. An article from 1982 similarly discussed that polypropylene can degrade from the formation of free radicals inside the body, and explained that "[t]he effects of these degradation processes will naturally vary, but generally there will be a change in average molecular weight, molecular-weight distribution, crystallinity and mechanical properties." A 1994 article describes the adverse biological effects of oxidative degradation of implant polymers, stating that the oxidative process "will augment any tissue injury due to the invading organisms. These highly reactive radicals generated by cellular mechanisms at or near the surface of

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"Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122. Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4. Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4. Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 29.4 (2007)

[301] Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122.

[302] Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res83B.1 (2007): 44-49.

[303] Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res83B.1 (2007): 44-49.

implanted polymers may contribute to damage of the polymer surface in the same fashion as established polymer degradation reactions by reactive radicals." The authors in the article entitled Biodeterioration/Biodegradation of Polymeric Medical Devices In Situ explained the cycle of foreign body response to a polymer implant material and degradation.[304] The authors explained that the "vicious cycle" results in "poor compatibility" and "can result in serious tissue response, where different enzymes and active species released from cells can damage the implant profoundly, the degradation products then possibly making the tissue response even worse."[305] Additionally, "mechanical stress may affect degradation" [306] as a result of loading under service. Wood et al summarized in their 2013 evaluation of mesh explants, "Unfortunately, polypropylene will degrade in an oxidizing environment, such as the environment during a foreign body response."[307]

Ethicon was aware of the degradation of the mesh yet did not do the longitudinal studies required under the international standard, ISO 10993-6 for prolonged biocompatibility testing in muscle. Ethicon scientist, Daniel Burkley has testified that mesh can degrade, degraded in the Ethicon dog study for its ABBREVO product, and that the degradation properties would be more elucidated if Ethicon had studied the effects of its actual product as permanently implanted in women.[308]

A consulting firm hired by Ethicon in 2011 reported that, "polypropylene can suffer from degradation following implant... a process which initiates after a few days post

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[304] Zhong, S.P. et al. *Biodeterioration/Biodegradation of Polymeric Medical Devices In Situ,* International Biodeterioration & Biodegradation, Vol. 130, 95 (1994).
[305] Id.
[306] Id, at p. 108.
[307] Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122.
[308] See deposition of Daniel Burkley (5/22/13) 108,206,315

implantation in animal studies."[309] Additionally, it was noted that the only change made to PROLENE since 1987 was the removal of Sanatanox, an antioxidant that could slow degradation

The foreign body reaction is also associated with the release of chemical messengers know as cytokines. These cytokines are responsible for recruiting more inflammatory cells. Cytokines are also well known to be associated with sympathetic nerve sprouting and chronic pain. Recent evaluation of vaginal mesh explants and abdominal mesh explants has demonstrated that vaginal mesh explants have 11 times the number of entrapped nerve fibers.[310] The continued degradation of the polypropylene mesh creates more rough surface area, more acute and chronic inflammation, recruiting even more macrophages and FBGCs, which cause more degradation, thus creating a problematic environment.[311] This is a viscous cycle of inflammation. The persistence of the foreign body reaction for the lifetime of the device indicates that the oxidation process is continuous. Klinge et al have demonstrated that implanted mesh continues to behave as a chronic wound eight years after implant.

Polypropylene Has an Adverse Effect on the Human Body

As described earlier the innate immune system recognizes and attacks foreign material. This is known as the foreign body reaction (FBR). Different materials are

[309] ETH.MESH.02589032 and ETH.MESH.07192929
[310] In The United States District Court For The Southern District Of West Virginia Charleston Division In Re: Boston Scientific Corp. Pelvic Repair System Products Liability Litigation MDL No. 2326 Iakovlev General Expert Report
[311] See e.g. Anderson et al, *Foreign Body Reaction to Biomaterials,* Seminars in Immunology 20 (2008) 86-100.

associated with different degrees of FBR. In the best-case scenario, the material is associated with only a minimal FBR and a mild, short-lived FBR occurs. In the worst-case scenario, a protracted severe FBR occurs. We are all familiar with the signs of a FBR, redness, warmth, swelling, pain, and loss of function. Indeed, medical students are given these words to memorize in Latin: rubor, calor, tumor, dolor, functio laesa.

In their paper arguing for decreasing the amount of polypropylene implanted (deceasing the total amount of polypropylene used in a piece of mesh), Cobb et al state "The long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial". This problem is well known in both the medical and scientific art. Multiple investigators have demonstrated the dramatic difference between a repair performed with native tissue and suture compared to one performed with polypropylene mesh. The authors demonstrated that, unlike the native tissue repair, the polypropylene (ppm) repair did not heal and continues to behave like both an acute and chronic wound.[312] Although decreasing the inoculum (the amount of polypropylene) may decrease the severity of the FBR, the problem of the severe FBR with ongoing acute and chronic inflammation persists and may even worsen.[313] Acute and chronic inflammation

[312] U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

[313] Arnaud Clavé & Hannah Yahi & Jean-Claude Hammou & Suzelei Montanari & Pierre Gounon & Henri Clavé. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261–270.
Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591. U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

is associated with both pain and loss of function.[314] Indeed the most common complication reported in the FDA's systematic review of transvaginal mesh are those associated with inflammation: extrusion and pain.

Of additional concern is the destructive effect of transvaginal mesh on surrounding tissues. In 2013, Liang et al reported on concerning effects of transvaginal mesh on human tissue. These investigators documented 20% decrease in collagen and 43% decrease in collagen.[315] This same year, 2013, Feola et al reported on the negative effects polypropylene mesh on muscle resulting in a deterioration of the biomechanical properties of the vagina.[316] Vaginal contractility decreased 80% following implantation with the GYNEMESH PS ($p=0.001$) and 48% after implantation of the lighter SmartMesh ($p=0.001$).

Dr. Brian Flynn, an Ethicon TVT-SECUR expert witness has cited a study by Falconer et al stating "Falconer also found minimal inflammation with the Prolene mesh and practically no tissue reaction even out to two years, while there was no difference between paraurethral connective tissue in biopsies from patients operated on with Prolene tape and in controls two years after surgery".[317] Dr. Flynn's comment is easily misinterpreted to mean that Falconer et al had demonstrated that the TVT PROLENE mesh does not destroy collagen and elastin and that it does not cause significant chronic inflammation. The Falconer study actually made no evaluation of the effects of the PROLENE material on connective contacted by the defective PROLENE. The Falconer

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[314] Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

[315] Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. BJOG 2013;120:233-43.

[316] Feola A, Abramowitch S, Jallah Z, et al. Deterioration in biomechanical properties of the vagina following implantation of a high-stiffness prolapse mesh. BJOG 2013;120: 224-32

[317] Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19-23.

study did not explant the mesh and examine the tissue surrounding the mesh and contacting the mesh. The Falconer et al study took biopsies from areas that were somewhere in the general vicinity of the mesh. In contrast, investigators interested in evaluating the effects of mesh on tissue, such as Liange et al, harvested the mesh-tissue complex. These investigators, on multiple occasions, demonstrated the destruction of both collagen and elastin by polypropylene mesh.[318] It should also be noted that Falconer et al made not attempt to evaluate the quality of the collagen or the ratio of type one to type three collagen.

It should also be noted that the Material Data Safety Sheet (MSDS) associated with the PPM resin of the TVT SECUR PROLENE mesh warned of a risk of cancer following implantation with the resin. "Polypropylene has been tested in laboratory rats by subcutaneous implantation of discs or powder. Local sarcomas were induced at the implantation site".[319] Although defense TVT-SECUR expert Jaimie Sepulveda reports "A Medline search for sarcoma and polypropylene does not yield a single case of sarcoma or malignancy due to the use of polypropylene material in humans", such a report would not be expected, as Ethicon has hid from the world the relationship between its PROLENE resin and Sarcoma.[320] Hence, no pathologist or surgeon would ever report on the presence of TVT device in a sarcoma patient. Although Dr. Sepulveda's opinion that "MSDS and rat studies reporting sarcoma formation after implantation of polypropylene discs and powder are not transferable to humans" is valid, he negates to point out the significance of his statement.[321] Firstly, the finding of risk in an animal model

[318] Liang R, Zong W, Palcsey S, et al. Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. Am J Obstet Gynecol 2015;212:174.e1-7. And BJOG. 2013 January ; 120(2): 233–243. doi:10.1111/1471-0528.12085.
[319] ETH.MESH.02026595
[320] See TVT-SECUR expert report of Jaime Sepulveda, Wave 3, pg26
[321] See TVT-SECUR expert report of Jaime Sepulveda, Wave 3, pg26

necessitates the evaluation in humans, not the hiding of the possible risk from its customers. At a minimum, a registry should have been created and labels updated. Secondly, Dr. Sepulveda's acknowledgement of the lack of transferability of the animal data to humans is an obvious admission that Ethicon had no justification for using its animal data to support TVT-SECUR. Indeed, Ethicon commercialized its TVT SECUR based, almost exclusively, on animal data.

Contraction and Fibrosis of Mesh

The pore size was defective. Decades in advance of the marketing of PPM mesh for transvaginal implantation; the abdominal hernia literature demonstrated a high incidence of severe inflammation, scarring, contraction and pain. Polypropylene mesh implantation in the treatment of abdominal hernias began decades prior to its use in vaginal surgery. Indeed, the original PPM implants used for vaginal surgery had obtained their 510K marketing approvals as abdominal hernia mesh implants or claimed such as predicates. Although PPM had been shown to decrease the recurrence rate of abdominal hernias, the loss of abdominal wall compliance and pain became a substantial problem. Prolonged patient discomfort and chronic pain were know to occur as often 20% and 50% of the time, respectively.[322] Looking at normal abdominal wall compliance, Junge et all reported that hernia meshes should have at least 25% vertical stretching and 15% horizontal stretching.[323] Ethicon indicated in 2006 "Elasticity in the range of 20–35% has been reported to match the compliance of surrounding tissues to avoid both extrusion of the

[322] ÕDwyer PJ, Kingsnorth AN, Molloy RG, et al. Randomized clinical trial assessing impact of a lightweight or heavy- weight mesh o n chronic pain after inguinal hernia repair. Br J Surg 2005;92:166–170.Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

[323] K. Junge á U. Klinge á A. Prescher á P. Giboni M. Niewiera á V. Schumpelick. Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants. Hernia (2001) 5: 113±118

material and patient discomfort".[324] Anyone skilled in the art should recognize that the vagina, an organ requisite to sexual intercourse and pelvic organ support, would need, at a minimum, an implant with similar compliance.

In 2007, Muhl et al reported on effective porosity. Muhl demonstrated that, in order to allow tissue ingrowth and prevent the bridging fibrosis and its resultant mesh contraction, poor sizes needed to remain greater than 1000 microns under the typical loads seen following implantation.[325] Muhl defined the pores remaining after such in vivo loading as "effective porosity". It is well known that PPM textiles, at time of implantation, are compliant. The surgical implantation immediately stretches the mesh as does the load created by in vivo pressure / activity. This stretch as been shown to change the pore shape and size. The result is always, a smaller effective pore. Yet, Ethicon chose not to measure its native poor size or effective poor size, and acknowledged it had neither a pore size requirement nor a validated measure of its Prolene mesh pore size.[326] Internal documents demonstrate that Ethicon was, however, aware of the defective nature of its size of its mesh, "There are two distinct pore sizes in the PROLENE 6 mil mesh (TVT). The major pore is about 1176 um.... The minor pore is about 295 um." [327] Even more concerning was the novel, off label, use of its Ethisorb product on it TVT-S. Ethicon chose to fuse its Ethisorb "fleece" over the ends of the TVT-S Prolene sling. Ethisorb is a device cleared for use on the human dura. It was never cleared for use on other tissue.

[324] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J.17.S1 (2006): 26-30.
[325] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, Publishe on line May 2007.2008. Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6.
[326] Smith Dep. (2-3-14) 729:1 to 729:12.
[327] ETH.MESH.00584175 (Ex. T-3583); ETH.MESH.00584179 (Ex. T-3581).

The Ethisorb label states that it is "is an impermeable sheet of material" that does not foster ingrowth but rather allows "on growth".

Ethicon was aware of the material defects and consequences thereof. Prior to the introduction of the TVT-S and TVT-O devices Ethicon knew of the material defects of its polypropylene mesh.[328] In 2003 Ethicon completed its 91 day rat study with its PROLENE mesh.[329] This study utilized a non-validated method of quantifying tissue reaction that was implemented by its employed PhD. This study noted that inflammation in all meshes persisted at 91 days. Ethicon's continued efforts to decrease the deleterious effects of its defective material are evidenced by its development of its ULTRAPRO product, cleared for marketing in 2004.

In December of 2007 Johnson & Johnson (Ethicon) completed its analysis of its PROLENE, PROLENE SOFT (GYNEMESH), and ULTRAPRO meshes.[330] This analysis implanted pigs and evaluated mesh contraction and tissue integration over a 13 weeks. Although all of the Ethicon meshes suffered severe contraction, ULTRAPRO contracted the least. All three mesh types showed "connective tissue bridged between the mesh nodes (pores)" and the deeper implants showed very little connective tissue. This is consistent with the later works of Liange et. all that found polypropylene mesh causes a severe destruction of both collagen and elastin.[331]

Ethicon's Awareness of the Defective Material

In 2010, Ethicon engineer and TVT-S inventor, Dan Smith, noted in an email sent to numerous Ethicon executives, "I personally believe that a PA (partially absorbable)

[328] See my Prolift and Prosima Opinions.
[329] ETH. M ESH.05512280-05512314
[330] ETH.MESH.01818397. An Investigational Study of Swine Models to Evaluate Mesh Contraction and Tissue Integration Over a 13 Week Period
[331] Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. BJOG 2013;120:233-43, Liang R, Zong W, Palcsey S, et al. Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. Am J Obstet Gynecol 2015;212:174.e1-7.

mesh of sorts, maybe Matrix (the Dan and Susan L. Matrix not the Hercules matrix) can play a future role in lowering complications rates but that requires lots of data and shifting of their current mental place regarding a PA mesh or a PA non-mesh material" and "The TVT+M PA mesh was a stepping stone to an end goal of a Matrix sling and the Scion delivery system was a means to address al of the unmet needs that existed in the SIS space".[332]

Summary Opinion of Material Defects

I state to a reasonable degree of medical and scientific certainty that the materials of the TVT-SECUR device were defective and such defects resulted in complications including but not limited to device failure, inflammation, contraction, chronic pain, chronic dyspareunia, urgency, urge incontinence, erosion, and fistula formation. I state to a reasonable degree of medical and scientific certainty that the PROLENE of the TVT SECUR device had inadequate pore size, degraded, contracted, lost elasticity, became rigid, and caused a chronic inflammation. I state to a reasonable degree of medical certaintly that Ethicon was aware of the defects of its TVT-SECUR PROLENE material.

The Device Was Defective

In May of 2008, one of the world's most experienced TVT-Secur surgeons, emailed the emailed Ethicon's World Wide Medical Director, World Wide Marketing Director, and Director of Research and Development:

> *"It becomes obvious that the TVT & TVTO were initiated by surgeons, while the TVTS was designed purely by engineers: the TVTS is very smart, regarding the mesh production and even more with the insertion mechanism. At the same time are the TVT & TVTO very "anatomical" and very "surgical", or may I say - very "surgeon's friendly".*

[332] ETH.MESH.06927248

In June of 2008 a meeting between Ethicon engineer and co-inventor of the TVT-S device, Dan Smith, Ethicon key opinion leader and consultant, Carl Nilsson , and other Ethicon representatives was transcribed.[333] The topic was Project Scion. This project appeared to focus on the development and deployment of an improved version of the TVT-S device.

Dr. Nilsson noted that there was a "Huge complication rate with TVT-S in Germany because of training concerns" and "There is no documentation that Mini-Sling is safer and with equal efficacy as TVT". He added:

- That the Hammock had much lower efficacy than the "U" method and "mini-sling hammock will never work"
- He questioned, "Will there ever be an exitless mini-sling that will work?"

Dan Smith stated that Ethicon would like DR. Nilsson to be involved in the development of the improved device. Dr. Nilsson indicated that a minimum of 1 year data would be needed prior to launch. Ethicon's Jason Hernandez noted that during a pre-clinical trial, all iterative changes would require an FDA IDE.

The group then reviewed the changes that would hopefully correct some of the defects of the TVT-SECUR device for use resulting in a "Next Generation Mini-Sling" for the obturator approach.

Ethicon Engineer Dave Smith noted that one size would not fit all (the proposed 12cm would be too big for Asian women and penetrate the obturator and it would be too small for bigger women). Dr. Nillson however stated that the sling would need to be

[333] **ETH.MESH.04048515**

14cm long to ensure that at least 1mm would be in the "end tissue". The goal was to get the sling into the obturator externus muscle but avoid the adductor muscle group. Dr. Nillson added "Will not use Laser-cut mesh!! Does not have the same stretch profile of Mechanical-cut mesh", and "TVT mesh is most forgiving because of stretchability".

Dave Smith noted that anchor would get holes, "Introduction of holes for tissue ingrowth". Dr. Nillson noted that an animal study would be needed to confirm ingrowth. Ethicon had believed since 2004 that such holes should be placed to facilitate ingrowth, yet no such feature was implemented.[334]

Dr. Nillson added that there was a "strong need for in-procedure test to know the precise adjustment (tension)"

The group then reviewed the changes that would hopefully correct some of the defects of the TVT-SECUR device for use resulting in a "Next Generation Mini-Sling" for the retropubic approach.

Although Dr. Nilsson had made it clear that it was important to utilize the rectus fascia for the fixation point of the sling ("There is no substitute for rectus fascia"), Ethicon's Dan Smith noted that the use of the rectus fascia would not be possible secondary to "IP" restriction (to stay within the claims of their mini-sling patents). Ethicon's patent claims required that its sling not exceed 10 cm in length. Hence, a sling long enough to enjoy the increased efficacy of rectus fascia fixation would be outside the scope of Ethicon's patent protection and open to marketplace competition. Furthermore, Ethicon's TVT-SECUR patent position required heavily on the IP surround the TVT-SECUR inserter, and inserter unlikely to work for fixation to the rectus fascia.

[334] See 2004 USPTO provisional patent application.

The Laser Cutting of The Mesh was Defective

With over 7 years of clinical experience with its mechanically cut PROLENE TVT-R product, Ethicon opted to use laser cut PROLENE for its novel TVT-SECUR device. The safety and efficacy of laser cut mesh (LCM) had been evaluated for either the TVT-R or TVT-S devices.

Allison London Brown, Ethicon's Women's Health and Urology World Wide Marketing Director, memorialized the move to laser cut mesh in her email to Ethicon engineer and inventor of TVT-S, David Smith.[335]

With regard to the rationale for changing the standard TVT-R to laser cut mesh, Ms. London-Brown explained:

> "The Market place was experiencing some challenges from surgeons who were using stiffer meshes with different construction, which had less particle loss and less mesh distortion during implantation".
>
> "In order to alleviate concerns/meet customer needs, the team identified 2 corrections: 1) a new sheath that created less drag during removal, 2) the use of Laser-cutting for processing which minimized particle loss as the material was some-what "melted" as it was cut, thus keeping most of the cut loops intact".

Interestingly, Ms. Brown added, "In order to claim the use of 7-year data and all clinical studies, the MCM and LCM needed to show similar properties with the physical properties being used as a proxy for the clinical needs". However, as noted already by Ms. Brown, the physical properties were very different. Yet, Ethicon would continue to rely on the TVT MCM data.

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[335] ETH.MESH.00858252

With regard to the rationale for using laser cut mesh in the TVT-S, Ms. London-Brown offered:

> "TVT SECUR is a new product/techinique and therefore there is little relationship to the 7-year database (TVT mechanical cut data) other then it is the same PROLENE mesh. Because a PDS yarn and Vicryl non-woven material are melded into the tips of the implant".
>
> "TVT SECUR team rational for the use of LCM (laser cut mesh) was to enable enable a higher quality and easier cutting process through the mesh and fleece, reduce particle loss, ensure the device length is not compromised during implant (no stretch), aid in operational efficiencies, therefor reducing COGS (lower manufacturing costs to improve profit)".

There was a "Marketing Need: Keep relationship with PROLENE mesh and launch a new technology"

Of additional interest is the fact that Ethicon chose not to file a 510K application for their new laser cut products stating, "Notification to the FDA is not required to implement this manufacturing change. The determination was based on the following assumptions: The indications for use will remain the same, clinical data will not be necessary to establish safety and effectiveness for this change, the results of design validation will not raise any new safety and new issues of safety and effectiveness, there will be no change to the existing performance specifications, there will be no decrease in sterility assurance limit. [336] However, Ethicon had already demonstrated its awareness that the LCM would have different technical characteristics then its MCM. Indeed, the decrease in elasticity was one of the main reasons Ethicon chose to use LCM. Furthermore, Ethicon internal documents demonstrated their awareness that the LCM

[336] ETH.MESH.00394544

was "about three times stiffer than the mechanically cut mesh".[337] Furthermore, Ethicon key opinion leaders including consultant Carl Nillson had warned Ethicon that they should not assume that LCM would have similar properties in vivo to MCM and that in vivo studies were required.[338] Yet it appears that Ethicon opted not to test the changes in elongation and rigidity created by laser cutting, qualities that have substantial effects on safety and efficacy.[339] The FDA requires notification, and, more likely than not, a new 510K application, if there is a change in the technical characteristics of the device. Under such circumstances, the manufacturer is required to demonstrate that the change does not result in a change in safety and efficacy. Ethicon knew that the technical characteristics had changed; yet opted not to notify the FDA. However, the 510 K process is not the guarantor of safety and efficacy. The burden of safety and efficacy remains the responsibility of the manufacturer. More important than notifying the FDA was the performance of animal testing, IDE trial, and clinical trials needed to demonstrate safety and efficacy. These were not done. Ethicon went on to conduct an experiment on tens of thousands of women, women who were implanted with the novel, experimental, laser cut TVT-S device. This experiment would result in the injury of many women and the finding that the changes caused by the LCM contributed in loss of efficacy and new complications.

In 2006, Ethicon, in its internal marketing document, Procedural Pearls and Frequently Asked Questions, notes,"GYNECARE TVT SECUR has been laser cut,

[337] ETH.MESH.01809080-ETH.MESH.01809081

[338] ETH.MESH.16416003

[339] ETH.MESH.00301741

which gives the mesh added resistance to distortion above the physiological range of normal forces".[340]

In 2008, Dr. Menachem Neuman, one of the world's most experienced TVT-Secur surgeons, emailed Ethicon's World Wide Medical Director, David Robinson, Ethicon's World Wide Marketing Director, Harel Gadot, Ethicon Engineer and first author on the TVT-Secur related patents, Dan Smith, and Ethicon's Director of Research and Development, Scott Ciarrocca.[341] The focus of this email was Dr. Neuman's findings with regard to TVT-S complications. Dr Neuman noted his experience. He had implanted 477 TVT-Secur devices. Dr. Neuman informed Ethicon that, compared to TVT-O, "there were more post operative obstructions, vaginal pain and tape protrusions". Dr. Neuman informed Ethicon "Most of the vaginal pain and lateral tape protrusion is caused by the increased tape stiffness - my feeling it is due to the laser cutting", "TVT-S is attached in general to more operative bleeding than TVT / TVT-O, and requires more force for introduction. The edges should be much thinner and rounder. This will reduce the vaginal wall injury ("button halls") as well", and "The detachment is not smooth enough , too many un-desired tape removal are reported". He added, that based on his experience, it had "become obvious" that the TVT-O and TVT devices were designed by surgeons with attention to anatomy and surgery, whereas the TVT-Secur device had been designed by engineers focused on mesh production and the mechanical insertion mechanism. The email was forwarded Ethicon's EMEA Director of Marketing, Andrew Beveridge, to Ethicon's Director of medical affairs, Axel Arnaud. That email stated, "lets discuss before taking action".

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[340] ETH.MESH.00157010
[341] ETH.MESH.03923121

In 2008, Ethicon engineer and TVT-Secur inventor, David Smith, noted "Most surgeons who use TVT products do not know if it what they use contains mechanically cut or laser cut mesh! Additionally, they don't know we have Laser cut TVT and TVT-O products on the market! (90% mechanically cut / 10% laser cut)". "TVTSECUR will NEVER get tighter once placed unlike most other slings to date, because of the short 4 cm of free mesh and laser cut design!".[342]

In or about 2008, Ethicon began PROJECT SCION, a project to improve the efficacy of and safety of the single incision sling.[343] Project consultant and TVT expert, Dr. Nilsson stated "Will not use Laser-cut mesh!! Does not have the same stretch profile of Mechanical-cut mesh".

That same year, 2008, Ethicon engineer and TVT-Secur inventor, David Smith, noted "For a mini-sling to be effective in the hands of "many" it should have a positive stretch in an upward direction, which will continue to support the urethra after placement, as did TVT and TVT-O". Smith adds, "The short laser cut mesh does not stretch the same as a full length mechanically cut TVT-O, or even as much as a full length LC TVT-O meshes". Herein, Ethicon's engineer and TVT-S inventor admits that the TVT-S sling, as designed, with its laser-cut minimal stretch, is not suited for "many surgeons" and should have been designed differently. The main difference that precluded stretch was the laser cutting.[344] Mr. Smith's concern for the laser cutting of mesh was further validated in his recommendation to use mechanically cut mesh for their improved hybrid sling, the MiniMe.

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[342] ETH.MESH.09911296

[343] ETH.MESH.04048515

[344] ETH.MESH.09911297

In summary, Ethicon had become aware that it's MC TVT PROLENE mesh was losing more particles than other sling meshes, that this particle loss had generated concern in the medical community, and that this particle loss was a potential cause of lost sales.[345] Based on such, Ethicon opted to offer a laser cut option to its TVT-R customers. However, it would continue to sell its MCM TVT products in a 9:1 ration over the laser cut version, without performing any testing or post market surveillance to access the effects on safety and efficacy. Ethicon opted to offer only LCM for its new and novel TVT-S device. This decision was predicated on a desire to have a less elastic sling and prevent particle loss. Unlike the rest of the TVT products that would continue to be sold, predominantly, as a MCM, only a laser cut mesh (LCM) was offered for the TVT-S device. As explained by Ms. London-Brown, this decision, at least in part, was secondary to the fact that they could not data-borrow from the seven years of TVT data, even if they used MCM, as the device had a different technical specification caused by the novel "melding" of Ethisorb onto the PROLENE. Ethicon knowingly opted to neither inform the FDA of the change to the technical characteristics of its mesh or perform the requisite animal labs, IDE trial, and clinical trials to demonstrate safety and efficacy of the LCM in its TVT-S product. It opted to assume safety and efficacy and experiment with the worlds population o of women. This experiment demonstrated that safety, efficacy, and women of the world were adversely effected by the novel LCM.

[345] ETH.MESH.00541379, ETH.MESH.02180826, ETH.MESH.03535750, ETH.MESH.00583446, ETH.MESH.04101014

Summary Opinion on Laser Cutting

I state with a reasonable degree of medical certainty that the laser cutting of the TVT-SECUR mesh changed the properties of the PROLENE sling causing more rigidity and less elasticity, caused problems with sling tensioning with resultant increase in failed surgery and resurgery, and more likely than not contributed to increased complication such as erosion and dyspareunia.

The Insertion Mechanism was Defective

The premarket Design Validation Lab demonstrated numerous problems with the inserter. Amongst various problems, surgeons had repeated difficulty with the release mechanism and wire (approximately one third of the cases associated with problems).

In 2008, Dr. Menachem Neuman, one of the world's most experienced TVT-Secur surgeons, emailed Ethicon's World Wide Medical Director, David Robinson, Ethicon's World Wide Marketing Director, Harel Gadot, Ethicon Engineer and first author on the TVT-Secur related patents, Dan Smith, and Ethicon's Director of Research and Development, Scott Ciarrocca.[346] The focus of this email was Dr. Neuman's findings with regard to TVT-S complications. Dr Neuman noted his experience. He had implanted 477 TVT-Secur devices. Dr. Neuman informed Ethicon that, compared to TVT-O, "there were more post operative obstructions, vaginal pain and tape protrusions". Dr. Neuman informed Ethicon "The detachment is not smooth enough, too many un-desired tape removal are reported". He added, that based on his experience, it had "become obvious"

[346] ETH.MESH.03923121

that the TVT-O and TVT devices were designed by surgeons with attention to anatomy and surgery, whereas the TVT-Secur device had been designed by engineers focused on mesh production and the mechanical insertion mechanism. The email was forwarded Ethicon's EMEA Director of Marketing, Andrew Beveridge, to Ethicon's Director of medical affairs, Axel Arnaud. That email stated, "lets discuss before taking action".

Of additional note, Ethicon TVT-SECUR Project Lead, Engineer, and inventor noted the following key design input in his initial TVT-SECUR proposal,

> *"The delivery device will provide the surgeon with a safe, easy to use. reproducible and anatomically designed instrument for implant insertion, placement and adjustment from the vaginal incision".*[347]

The inserter was never found to be easy to use, the designed method of use was not easily reproduced, and placement was found to be difficult. As note elsewhere herein, perhaps the largest amount of intellectual property protecting the TVT-SECUR was related to the Inserter developed by Mr. Smith and his team. Components of this patent protection included a penetrating and cutting tip.

The TVT-S device had a hard cutting tip that Ethicon believed was responsible for increased bleeding. David Smith, Ethicon engineer and an inventor of the TVT-S device noted, when describing a next generation TVT-S with an unchanged tip, "The device will still have a cutting edge and competitors will site increased bleeding verses a non-cutting tip even if bleeding is reduce due to the pathway being closer to the ischial pubic

[347] ETH.MESH.07898861

ramus".[348] Mr. Smith, when describing an in-development longer version of the TVT-S (the SCION sling), noted that it would be changed such that it would have an absorbable, not pointy and hard tip. He added "Device will have a round body and no cutting edges". Mr. Smith, in a email to Ethicon's World Wide Medical Director and others described his frustration with the slow progress being made to improve the TVT-Secur product. "What is frustrating to me is that this project has been around long enough to see 3-5 generations of top management leadership, each bringing new views into play".[349] "EWH&U could have had an improved TVT SECUR obturator only version in 2008 to address bleeding and consistent placement, but TVT SECUR was considered a failure and did not warrant line extensions." "EWH&U could have had a Scion SIS device with PP tips and shaped PP mesh in late 2009/early2010, but we needed to have more features so absorbable tips were added, increasing scope, timing and COGS".

Ethicon was aware of the bleeding problem associated with the TVT-S and trained its sales representatives to counter the concerns of bleeding voiced by surgeons.[350] In November of 2006, Ethicon's Great Britain Country Directory, Ralf Gotter, emailed Ethicon's Europian Marketing Manager and Ethicon's Worldwide Director of Medical Affairs. The Subject of the email was "The more procedures the more problems". In this email, Mr. Gotter reported "I would like to inform you that we are facing some problems within the last day with TVT SECUR. Strong bleeding and or haematoma in 5 cases".[351] Mr. Gotter continued, "We see no correlation with training hospitals or regions. Problems appeared in both. Hammock and U-position. Especially the first issue is the most risky for us ".

[348] ETH.MESH.09911299
[349] ETH.MESH.06927248
[350] ETH.MESH.01677076
[351] ETH.MESH.03921612

Summary Opinion on the Inserter

I state with a reasonable degree of medical certainty that the TVT-SECUR inserter was defective, that the TVT-SECUR inserter design caused surgeons to dislodge the sling resulting in surgical failures, that the TVT-SECUR inserter design contributed to the bleeding complications, bladder injury, and urethral injury, that Ethicon was aware of the defectiveness of the design, and that Ethicon, more likely than not, chose not to change the design secondary to financial consideration included those of patent protection and development costs.

The Length and Anchoring Was Defective

In or about 2008, Ethicon began PROJECT SCION, a project to improve the efficacy of and safety of the single incision sling. Ethicon internal documentation of this project includes advice from their consultant expert surgeon, Dr. Nilsson, that the rectus fascia should be used and that anchors would hence not be needed ("fixation should be along the length of the tape").[352] However, Ethicon engineer Dan Smith explained that such would not be possible secondary to the constraints of their business model (they needed to stay within the claims of their mini-sling IP). Based on such, the anchors would remain and the tape would be lengthened to 12-14 cm, in order to penetrate muscles (and allow better fixation). This need for a longer sling was further validated in the Ethicon development of the above noted SCION sling (11-14 cm) as well as the MiniME sling (a hybrid of the TVT-O and TVT-S) at 11 cm.[353] This would later be commercialized as the TVT Abrevo.

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[352] ETH.MESH.04048515
[353] ETH.MESH.09951746

As discussed elsewhere herein, the "fleece" covering of the anchor was impermeable and prevented tissue ingrowth. In or about 2008, Ethicon began PROJECT SCION, a project to improve the efficacy of and safety of the single incision sling. Ethicon internal documentation of this project includes a stipulation by Ethicon engineer David Smith that the anchor of the new sling would have holes for tissue ingrowth. Project consultant and key opinion leader, Dr. Nilsson, added that an animal lab would be needed to confirm tissue ingrowth.

In 2008, Ethicon's internal, confidential, presentation demonstrated Ethicon's awareness of its defective anchoring mechanism. This presentation was on prototype slings Ethicon was developing to replace its failing TVT-Secur device. The presentation asks the following question, "What will be our value proposition (for its new hybrid slings) should MiniArc (or any other exit less sling) get the same efficacy as TVT O/TVT?" Ethicon herein acknowledges that its TVT-Secur device has inferior efficacy and that it has considered the possibility that the failure of its TVT-S device is at least in part secondary to the experimental, non-barbed, Ethisorb ends and experimental introducer system (The AMS MiniArc utilized a conventional barbed anchor and placement needle).[354]

In 2008, Ethicon Engineer and TVT-Secur inventor noted that the TVT H should have been designed as a 10 cm sling. "TVT SECUR should have been launched as two separate products,"U" being 8 cm long and"H" being 10 cm long and each having there own IFU. Although 8 cm will work as we have seen, this would have reduced the misuse, confusion and reduced the learning curve".[355] Mr. Smith's conviction for a longer TVT-

[354] ETH.MESH.09951746
[355] ETH.MESH.09911296

Secur is further noted in his description of the "Next Generation TVT-SECUR. He notes that it shall be 10cm in length and will stretch slightly more.[356] Mr. Smith's concerns over length are further noted in his recommendation of Ethicon's development of its new MiniMe sling, "12 which should stretch to 14cm". Mr. Smith also noted that "For a mini-sling to be effective.. It must have sufficient holding ability with a high initial slip value, and be easily/reliably placed in multiple tissue structures". Although Ethicon did have animal day sufficient to petition the FDA for and IDE to test the holding ability of its TVTx anchor in the human vagina, Ethicon had no such animal data on the TVT-S anchor (unlike the TVTx, the TVT-S anchor had no barbs) and pre-clinical human validation did not occur. Mr. Smith herein has indicated that the TVT-S anchor is not sufficient. As noted elsewhere here in and as evidenced by the MiniMe and Scion sling projects as well as the commercialization of the TVT-Abrevo by Ethicon, the TVT-S anchors were defective.

Ethicon's only in vivo evaluation of the pull out force for its TVT-SECUR concept was performed with the TVTx prototype. This TVT-SECUR prototype utilized a barbed "arrow-head" fixation end. The arrow-head's ability to resist pull has been validated by centuries of use inside and outside of the world of medicine. Ethicon performed an in vivo rabbit study to evaluate the arrow-head anchor of the C.R. Bard Ajust mini sling.[357] This study found the Ajust design to provide significantly better resistance to pullout than its TVT-SECUR immediately after insertion and at both the 4 week and 12 week intervals. Adjust's immediate resistance to pull out was almost 10 greater than the TVT-SECUR. Resistance at 4 weeks was almost 4 x greater than the

[356] ETH.MESH.09911298
[357] ETH.MESH.01186612

TVT-SECUR. Resistance at 12 weeks was almost 2 x greater than the TVT-SECUR. My two-year MiniTape improvement project demonstrated the importance of resistance to pullout for the first 1-2 weeks. This is the time period in which the Ajust anchor demonstrated 4-10 x the resistance of the TVT-SECUR experimental fleece anchor.

This rationale for using the Ethisorb anchor, a rationale discussed in more detail elsewhere herein, was based on profitability rather than clinical outcomes. Both the patent portfolio and numerous comments of TVT Project Lead and inventor, Dan Smith, evidence this. In 2006 Dan Smith presented the TVT-SECUR project to his team. As the answer to why the TVT-SECUR would beat the competition, "Why we will win", Mr. Smith offered "The Uniqueness of Ethisorb" and Smith continued to state that secondary to the proprietary nature of the Ethisorb "The use of Ethisorb may give us an edge".[358]

Summary Opinion on the TVT-SECUR Length an Anchoring Mechanism

I state with a reasonable degree of medical certainty that the TVT-SECUR length was defective, Ethicon knew the length was defective, Ethicon refused to change the length secondary to financial consideration, and that the defective length caused women harm. I state with a reasonable degree of medical certainty that the TVT-SECUR anchor ("Fixation End") was defective, Ethicon knew the anchor was defective, Ethicon discarded an anchor likely to have been effective secondary to IP related financial concerns, Ethicon failed to validate the defective anchor prior to commercialization, and that such defect and failure resulted in harm to women.

[358] ETH.MESH.07898863

The Codman Ethisorb Dura Patch was Defective

The fixation ends of the TVT-SECUR were created by sandwhiching the laser cut PROLENE mesh between two pieces of thermally welded CODMAN ETHISORB Dura Patch. This is a proprietary "fleece" made of (polyglactin 910) suture yarn and PDS suture (poly-p-dioxanone). The Dura Patch product is cleared by the FDA with the intended use of bridging defects in the dura mater of the central nervous cystem (e.g. brain and spinal cord). This requires the Dura Patch to be water tight to prevent leakage of cerebral spinal fluid. Indeed, Ethicon's label for its Dura Patch notes that it is an impermeable sheet of material. Ethicon notes that a PDS film provides this quality. Mr. Smith, the TVT SECUR Project lead and inventor pointed out the PDS can take up to 180 days to absorb.[359] As noted elsewhere in this monograph, a mesh product should maintain pores of at least 1000 microns to allow tissue ingrowth and prevent bridging fibrosis. To the extent that the PROLENE mesh may have maintained some pores greater than 1000 microns prior to loading, the impermeable, water-tight, Ethisorb Dura Patch obliterates porosity. Consistant with this, Ethicon's Ethisorb Dura Patch label touts tissue "on-growth" rather than in-growth. The obliteration of porosity not only favors bridging fibrosis and contraction, but precludes the entry of white blood cells need to fight infection.

Dan Smith, TVT-SECUR Project Lead and inventor in his TVT-S proposal, noted "*ETHISORB will be unique to TVTx and will provide strong market differentiation on proven products. ETHISORB is absorbed in approx. 30-60 days and PDS can take up to 180 days for complete absorption.*"[360]

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[359] ETH.MESH.00157010
[360] ETH.MESH.07898861

Prior to commercialization of the TVT-SECUR product, the impermeable CODMAN ETHISORB Dura Patch had never been tested in the human vagina. The ability of the the heat welded ETHISORB Dura Patch to fixate the TVT-SECUR device had note even been validated in a living animal. A barbed version, the TVTx had been tested in a sheep. However, the any fixation may have been secondary to the barbs. In 2006 Ethicon launched its TVT-SECUR product without a single bit of human data demonstrating the safety of the heat welded ETHISORB dura Patch implanted in the human vagina. Based on what was already known about micorporous implants, the covering of the TVT-SECUR mesh, already with inadequate effective pore size with the impermeable heat welded ETHISORB Dura Patch would be expected to result in fibrosis, inflammation, rigidity, infection and pain. Of additional note, Ethicon brought the TVT-SECUR to market without any living animal or human data to validate the effectiveness of the non-barbed heat welded ETHISORB Dura Patch fixation ends.

As noted herein as well as elsewhere in this monograph, the driving force for the use of the experimental ETHISORB Dura Patch fixation ends was “market differentiation” and patent protection. As also noted elsewhere herein, Ethicon rushed to market without demonstrating safety or efficacy.

Summary Opinion on the Use of The Codman Ethisorb Dura Patch

I state with a reasonable degree of medical certainty that the experimental thermally welded CODMAN ETHISORB Dura Patch fixation ends of the TVT-SECUR were defective, increased the risk of fibrosis, contraction, infection, and pain, that Ethicon failed to perform any human trials to demonstrate either safety or efficacy for its

new intended use, that Ethicon failed to warn of the experimental nature of this use of its CODMAN ETHISORB Dura Patch, that such experimental use was motivated by financial gain, and that such experimental use and failure to warn both physicians and patients resulted in harm to women.

The Teachings of Ethicon were Non-factual and Misleading

Ethicon's internal marketing document "Procedural Pearls & Frequently Asked Questions"[361]

This internal Ethicon document provides Ethicon representative with answers to "frequently asked questions". These answers are misrepresentation of the material facts and are misleading.

1. How does the GYNECARE TVT SECUR device stay in place?

   Answer: The device uses a unique combination of absorbable fleece bonded onto the Prolene* polypropylene Mesh with a layer of PDS. This combination stiffens the implant end and creates sufficient fiction to secure the mesh where placed. This frictional function is similar to that created by conventional GYNECARE TVT. However, much less material is needed for the new idea since the standard GYNECARE TVT gets smaller as it stretches, while GYNECARE TVT SECUR retains its shape and stiffness until tissue in-growth occurs".

   This is a misrepresentation of the facts that, more likely than not, would lead the recipient thereof to believe that the TVT-S is should be as effective as the TV. In

[361] ETH.MESH.00157010

2006 Rezapour et al published their preclinical trial which aimed at evaluation the performance of the TVTx mesh in a sheep model.[362] I am unaware of any other study that compared the friction of a single incision sling to TVT. This study did not provide no comparative information between the TVT-S friction and TVT friction. The studied single incision sling, TVTx contained a barbed end, unlike the TVT-S, which may have been responsible for the friction. Additionally, this study by Rezapour utilized a much longer sling (more material) than TVT-S and included barbed ends. Hence, there was no data therein that could support the statement that "much less material is needed".

2. "Does the GYNECARE TVT SECUR enter the obturator space when placed in the "H" position?"

Answer: When properly positioned, each absorbable end of the GYNECARE TVT SECUR System is located in the obturator internus muscle. The ends should be in light contact with the ischial pubic ramus, thus serving as a permanent structure before and after tissue in-growth. Neither the inserter nor the implant penetrates the obturator membrane. Therefore, the obturator bundle should not be at risk of injury.

[362] Rezapour, Masoumeh, Giacomo Novara, Peter A. Meier, Joerg Holste, Susanne Landgrebe, and Walter Artibani. "A 3-month Preclinical Trial to Assess the Performance of a New TVT-like Mesh (TVTx) in a Sheep Model." *International Urogynecology Journal* 18.2 (2006): 183-87.

This is a misleading answer that does not address the point of the question. This is a question that would be asked by a surgeon who is concerned about adverse events associated with obturator space penetration. The answer fails to state that it was unknown at the time how often the TVT-S was properly placed, how often it was incorrectly placed, and how such misplacement could cause harm. Indeed, In 2009, Hubka et al published their cadaveric study, Anatomical relationship and fixation of tension-free vaginal tape Secur, demonstrating that correct placement might occur in only 20% of surgeries. Furthermore, Hubka et al demonstrated that the tip of the introducer could come within 7mm of the obturator nerve and closer to the blood supply of the obturator internus muscle. The TVT-S tape is wider than that, 11 mm. The answer, more likely than not, would create a false sense of safety amongst surgeons.

3. When would I place the device in the "U" position and when would I place it in the Hammock position?

Answer: Placement of GYNECARE TVT SECUR is up to the discretion of the surgeon based on his or her preference and the condition of the patient. The GYNECARE TVT SECUR System is intended to be use in the same applications as either GYNECARE TVT or the GYNECARE TVT Obturator.

This answer fails to disclose the facts, and, in doing so, misleads the recipient of this answer to believe that the TVT-S is a reasonable substitute for the TVT and TVT-O devices. Ethicon had not tested the efficacy of the "H" vs. the "U" method. Ethicon had not performed any controlled prospective comparison of the TVT-S "H" and "U" methods vs TVT or TVT-0. Later studies would demonstrate that the "U" and "H" methods were not equally efficacious, had unique risks, and were not as efficacious as the TVT or TVT-O devices. Indeed, later in this same document, Ethicon, without explanation, notes that the "U" method is "not our preferred positioning". One example of what a factual answer is, "We have designed these devices in hope that they may be used as a safe, efficacious, alternative to the TVT-O and TVT devices. However, at this time we have not performed a prospective evaluation of the methods".

4. "Can you perform GYNECARE TVT SECUR in combination with prolapse surgery?"

Answer: Yes, it has the same indications as GYNECARE TVT and GYNECARE TVT Obturator. It is up to the surgeon to determine the order of the surgical procedures, however most indicate it should be placed after prolapse repair.

This answer fails to disclose the facts, and, in doing so, misleads the recipient of this answer to believe that the TVT-S may be used effectively in patients with

> prolapse, a behavior that most likely lead to increased failures among treated patients. The fact, the truth, was that Ethicon had no idea if the TVT-S procedure would be adversely affected, have lower efficacy, in patients with pelvic organ prolapse. No meaningful data was available. Furthermore, understanding the nature of the procedure the invented in house, Ethicon should, at a minimum, have offered a concern for impaired efficacy in this patient population. Whereas the referenced TVT and TVT-O slings are anchored or attached to healthier fascia that is outside the pelvis, the TVT-S device depends on pelvic tissue for such attachment. This tissue is weakened amongst patients with prolapse. It appears as though Ethicon was aware of this concern. In 2011, Its Worldwide Director of Medical Affairs, Dr. Hinoul, conducted a RCT with TVT-S, excluding all women with greater than stage two prolapse.

Ethicon's "New Hire Certification Exam Key" teaches its sales representatives the answers to the potential questions of surgeons.[363]

> This document teaches the sales representative to state that the "TVT-SECUR one-year study found 97% efficacy and 88% cure.
>
> This misleads the surgeon to believe that they can expect an 88% cure rate.
>
> However this teaching fails to provide that this cure rate was not achieved with the IFU method and fails to provide that this cure rate was determined by phone calls to subjects (not examinations).[364]

[363] ETH.MESH.01677075
[364] This increased cure rate was noted in only 50 patients operated on with the method of Neuman.

The Training Provided By Ethicon Was Defective

In December of 2006, Ethicon's Worldwide Medical Director, in an email correspondence related to inconstant surgical outcomes, noted,

> Having said that, it is just as clear that we are having some type of training problems and in order to prevent widespread negative talk, I think we must take palliative steps quickly.[365]

As part of this same email chain, Worldwide director of Medical Affairs, Axel Arnaud, stated:

> If a significant number of surgeons is not following what is written, we need to understand why? The answer might not just be that they are all undisciplined. They might also have hard time to understand the procedural steps from the material they received during their training.
>
> We cannot ignore that some surgeons who have been able in the past to successfully perform TVT and TVT-O are now struggling to achieve the same results with Secur. I wish the solution would just be to tell them to get back to their homework, but I am not sure it is the best one. All our best efforts should be focused on their difficulties to achieve consistent results.
>
> The reality of the field is that some surgeons, including KOL's who have been correctly trained and who have passed the learning phase, are raising concerns about the efficacy of TVT Secur. They have hard time to achieve consistently good results with the device. They are asking for clear recommendations about the way to perform the procedure.

Following revised training by Dr. Lucente, complaints from Australian surgeons quadrupled. Ethicon noted that additional complaints expected to be four times that received.[366] This would result in a 16 fold increased complaint rate from Australian surgeons following re-training. Ethicon noted that the Australian surgeons continued to

[365] ETH.MESH.01784428

[366] TVT-Secure Quality Board PowerPoint presentation. ETH.MESH.01758770. See also ETH.MESH.00642325 (Email discussing product design and training issues, Ethicon employ Dr. Khoo acknowledges that if products are not properly rolled out and physicians adequately trained, patients end up getting "the short end of the stick").

report greater than a 50% failure rate following re-training. Ethicon noted that it should not train any new physicians until revised material were available. Although Ethicon's internal document stipulated that is should not train any more surgeons until revised materials were available, I can find no evidence that training was suspended. Furthermore, this same internal document states, *"Need to keep product on the market to train people"*.

In 2007, Ethicon's Australian Medical Director reported on the findings of its Key Opinion Leader, Professor Frazer.

Regarding re-training on key points. Prof Frazer said that he disagreed with the company calling it re training: 'This isn't re-training. This is how things always should have been done and how we always should have been trained.' Also 'the nuances I have been learning in the last two weeks were never what I was taught in the beginning.' Even so, he is 'not yet convinced that even with these changes the device is going to be as successful as TVT-0 and TVT-Retro-pubic. I haven't yet seen enough evidence. Even Vince Lucente's data isn't yet convincing to me.[367] In October of 2007 Teng Chuan Khoo, J&J's Vice President of Strategic Medical Affairs and a regulatory affairs expert informed Ethicon's World Wide Medical Director David Robinson "*The responsibility of controlling the adequacy of training is critical and this has also been the subject of discussion between Aran (Ethicon's Australian Medical Director) and myself*".[368] He additionally note that adequate training was necessary to "*rollout a device such that patients do not get the short end of the stick*".

In June of 2008, an Ethicon internal document noted a "*Huge complication rate with TVT-S in Germany because of training concerns*".[369]

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[367] ETH.MESH.00327062
[368] ETH.MESH.00642327

[369] ETH.MESH.04048515

TVT-SECUR expert witness, Dr. Brian Flynn, referring to the TVT-SECUR IFU in his TVT-SECUR expert report notes that the IFU states "Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in implanting the Gynecare TVT Secur System before using.," and adds his opinion, *"The IFU specifically tells physicians that they should be trained on the device. This additional training may come from Ethicon or from other surgeons experienced with the TVT or similar midurethral slings*".[370]

Summary Opinion of TVT-SECUR Training

I state with a reasonable degree of medical certainty that the TVT-SECUR training was defective, Ethicon was aware of such defect, physician's relied upon Ethicon for training, Ethicon failed to correct training defects, and Ethicon knowingly experimented on women by choosing to keep its TVT-SECUR product on the market with defective surgeon training.

Alternatives to the TVT-SECURAs noted in my opening chapter that reviewed the topic or urinary incontinence and treatment options, prior to the launch of the TVT-SECUR product there were (and still are) numerous effective options for the treatment of stress urinary incontinence. The systematic reviews of the medical literature had demonstrated that traditional natural tissue slings and native tissue suture device repairs such as MMK and Burch Procedures (AKA Colopurethropexy) had similar efficacy to the newer synthetic midurethral slings. The systematic reviews of the medical literature had demonstrated that the retropubic and obturator slings had similar efficacy. Efficacy

[370] TVT-SECUR expert report of Dr. Brian Flynn pg 42

ranged from 80% to 90%. Defense TVT-SECUR expert witness Dr. Brian Flynn cites an 11 year TVT (retropubic) subjective cure rate of 93%-95%.[371] Complications of the non-mesh surgeries were uncommon and almost always reversible. As noted by Ethicon's professional education deck, serious complications of full-length retropubic slings were rare.[372] This sentiment is echoed in the opinion of Ethicon's TVT-SECUR expert witness Dr. Brian Flynn who cites multiple studies demonstrating an absence of serious TVT complications and also notes that TVT bladder perforations were inconsequential.[373] Of additional note, light weight, large pore mesh (effective pore size over 1000 microns) has been shown to be a safer alternative to PROLENE mesh.[374] Indeed, as noted elsewhere herein, Ethicon planned to introduce an Ultrapro sling that would, after absorption, provide a permanent implant that was much lighter and had larger pore size. Ethicon never introduced this improved safer alternative.

Early experience with soft-tissue anchor single incision slings was disappointing and efficacy equal to existing midurethral slings was unlikely.[375] Indeed, Ethicon's internal documents demonstrate a quest for equal and not superior efficacy. This was never achieved. From the time of market launch until the time of withdrawal from the market, there remained numerous safer and more effective options for the treatment of stress urinary incontinence.

On June 22nd of 2008, Ethicon's Worldwide Group Marketing Director, Harel Gadot, emailed a presentation entitled "Next generation sling. Evaluating opportunities, considering risks" to numerous Ethicon employees including its World Wide Medical

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[371] TVT-SECURE expert report of Dr. Brain Flynn pg 19
[372] ETH.MESH.00136850
[373] TVT-SECUR expert report of Dr. Brian Flynn pg 19
[374] Okulu, et al., Use of three types of synthetic mesh material in sling surgery: A prospective randomized clinical trial evaluating effectiveness and Complications; Scandinavian Journal of Urology, 2013; 47: 217-224
[375] See discussion of Ethicon's 5 week human trial data herein. See my 2003 experience described herein.

Director and Director of Research and Development. Key portions of the documentation are reviewed herein.[376]

The presentation then provided a discussion of two sling concepts under development, "MiniME" (Mini TVT-O) and "SCION" (Exit less TVT-O / TVT R). Both slings were longer then the TVT-S and would penetrate more deeply into muscle. The MiniMe was an 12 cm obturator sling that was threaded, at its ends, with a removable non-absorbable suture (used for adjustment). The sling would penetrate the obturator space, but would not penetrate the adductor space (Adductor magnus, brevis, and gracilis muscles). Ethicon obtained marketing clearance for its MiniME sling in 2010, then named the TVT ABBREVO.

A Timeline of Important Quotes

2006

In 2006 Rezapour et al published their preclinical trial that aimed at evaluation the performance of the TVTx mesh in a sheep model.[377] This was a prototype mini-sling that was used to validate TVT-S. TVTx was a longer version of the TVT-S device with barbed Ethisorb ends.

> *"The data collected in this study show the proof of principle of TVTx and could support the realization of clinical trials with the TVTx mesh".*

A 2006 email from TVT-Secur Project lead Dan Smith to Axel Arnaud, World Wide Director of Medical Affairs.

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[376] ETH.MESH.09951746

[377] Rezapour, Masoumeh, Giacomo Novara, Peter A. Meier, Joerg Holste, Susanne Landgrebe, and Walter Artibani. "A 3-month Preclinical Trial to Assess the Performance of a New TVT-like Mesh (TVTx) in a Sheep Model." *International Urogynecology Journal* 18.2 (2006): 183-87.

> *"Based on your strong position as stated in bullet#4 above to rewrite the TVT SECUR IFU, I will unfortunately need to remove myself from this project, due to the limited time I have to support this effort. Therefore I wish you much success in the noble endeavor, and I will try to make myself available on a limited basis to answer any questions your new team may have".*[378]

2007

Han et al reported one-month follow-up of thirty women treated with the TVT-S device.[379] The authors reported a 67% cure rate (by negative stress test) and concluded,

> *"The one-month cure rate was rather low when compared to TVT and TVT-Obturator". These authors also note a 6.6% incidence of bladder injury.*

Friedman presented his plan for analysis of his TVT-S vs TVT-O data.[380] Friedman reported that

> *"virtually no scientific papers appeared in the literature" with regard to the efficacy of the TVT-S device.*

Reflecting back on 2007, Tincello et al, in discussing TVT-World, reported ,

> *"The TVT Worldwide Observational Registry for Long-Term Data was established in 2007 to provide the real world outcomes of a single incision sling"* and *"At that time there were only 2 small published studies showing the 3-month*

[378] ETH.MESH.01784431
[379] Han, H.C., Shukiman, I., Lee, L.C., TVT Secur® In Treating Female Stress Urinary Incontinence : Early Experience. . Int Urogynecol J (2007) 18 (Suppl 1):S107–S244
[380] Friedman, M. TVT-S Vs TVT-O : Randomized, Prospective Comparative Study Of Intraoperative Complications, Perioperative Morbidity And Short-Term. Int Urogynecol J (2007) 18 (Suppl 1):S107–S244

outcome in only 24 patients, including 11 with a U insertion and 13 with a ham-mock insertion".

2008

Martan et al presented their prospective 6 month data.[381] They noted a objective cure rate of only 62% and an 8% incidence of erosion. The authors concluded,

"The tape used in the TVT-S procedure is less elastic than that used in the TVT or TVT-O procedure, so this tape must be slightly over-tightened, which means the tape is not tension- free. These steps are crucial for the curative effect".

Debodinance and authors including Lucot, Cosson, Villet, and Jacquetin (a group that included the inventor of TVM and some of the most experienced Ethicon KOL's in the world) reported on their one-year prospective observational study.[382] These authors reported one-year efficacy ranging between 40% and 72% with almost 60% of patients lost to follow-up. The authors concluded,

"The result are less good than TVT or obturator route procedure".

[381] Martan A, Svabik K, Masata J, El-Haddad R, Koleska T, Pavlikova M
IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)
[382] Debodinance P, Lagrange E, Amblard J, Yahi H, Lucot J, Cosson M, Villet R, Jacquetin B
IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

Smith et al presented their industry funded two-year prospective observational study of the TVT-S device.[383]

> The authors pointed out there was *"little published data with regard to the safety or efficacy of single incision mesh slings for USI"*.

> Smith et al concluded "*The short segment tape has a substantially lower cure rate than reported for full length tapes such as the TVT and the cure rate rapidly declined over the two year follow up period, especially during the first six months"*.

Neuman published his perspective observational case series on the TVT-S device.[384] Neuman concluded,

> *"(TVT-Secur is) associated with mild early safety and efficacy problems", "[T]he novel TVT-SECUR's actual place among TVT and TVT- related procedures should be determined with randomized prospective longitudinal comparisons"*.

Roovers and co authors, including Ethicon's medical director Pete Hinoul, presented their results of their Ethicon sponsored six-month prospective evaluation of the TVT-S device. The authors concluded,

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[383] Smith A, Hilton P, North C, Ali-Ross N. IUGA 33RD ANNUAL MEATING, TAIPEI, TAIWAN, ORAL PRESENTATIONSInt Urogynecol J (2008) 19 (suppl 1)

[384] Neuman N (2008) Perioperative complications and early follow-up with 100 TVT-Secur procedures. J Minim Invasiv Gynecol 15:480–484

"[W]e advise to await the results of the ongoing TVT-O/TVT-S trial before selecting TVT-Secur as first choice surgical treatment in patients with SUI".

The U.K. NICE group published their guidance on Single Incision Slings[385]:

"*Current evidence on the safety and efficacy of single-incision sub-urethral short tape insertion for stress urinary incontinence in women is inadequate in quality and quantity. Therefore this procedure should be carried out only in the context of research studies or through submission of data to a national register".*

"This procedure should only be carried out by a clinician with specific training in this technique".

"Systematic long-term follow-up is essential. The Institute may review the procedure upon publication of further evidence".

2009

Three years after the intial marketing of TVT-S, Hubka et al published their anatomic study of the product.[386]

[385] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 262. Single-incision sub-urethral short tape insertion for stress urinary incontinence in women. May 2008. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG262

[386] Hubka, Petr, Jaromir Masata, Ondrej Nanka, Milos Grim, Alois Martan, and Jana Zvarova. "Anatomical Relationship and Fixation of Tension-free Vaginal Tape Secur." *International Urogynecology Journal* 20.6 (2009): 681-88.

> *In 2008, Hubka et al published their cadaveric study, Anatomical relationship and fixation of tension-free vaginal tape Secur. In their abstract, the authors noted "So far, there has not been any anatomical study focussed on TVT-S, so we decided to investigate anatomical localization, assess the safety of this method and examine the fixation site of the TVT-S tape in the light of reported haemorrhagic complication during TVT-S"*

In 2009 North et al published their prospective observational study of women undergoing implantation of the original, unmodified Minitape (without my modification).[387] Sixty women were implanted between 2002 and 2006. Two women declined all follow-up appointments. The cure rates (negative one hour pad test) were 33% at one month, 21% at six months, 16% at one year, and 10% at two years. North et al noted,

> *"A larger study would be required to confirm the safety of the device, which is not appropriate given the level of efficacy demonstrated".*

> *"Although it may not be appropriate to extrapolate the results from this study to all miniaturized versions of TVT, they do indicate that such new tapes should undergo robust clinical evaluation before they are used outside the clinical trial setting".*

[387] North, C., Hilton, P., Ali-Ross, N. and Smith, A. (2010), A 2-year observational study to determine the efficacy of a novel single incision sling procedure (Minitape™) for female stress urinary incontinence. BJOG: An International Journal of Obstetrics & Gynaecology, 117: 356–360.

Krofta et al[388] presented their one year prospective observational data on 73 women undergoing implantation of the TVT-S device. The authors reported a 58% objective one-year cure rate. The authors reported a 6% incidence of mesh extrusion, an 11% incidence of repeat surgery for SUI within one year, a 23% incidence of de novo urge incontinence. The authors concluded,

> *"TVT-S appears to be less effective than TVT or TOT for surgical treatment of stress urinary incontinence in women. There was a surprisingly high incidence of urge incontinence and mesh erosion".*

2010

Jeffrey et al present their systematic review of the literature on minislings.[389]

> *"Despite the widespread use of these products, there is unfortunately limited data available on the efficacy and complications of these procedures".*

Cornu et al published their prospective evolution of the TVT-SECUR device, providing greater longitudinal follow-up than previous investigators (at 30 months cure had decreased to 40%).

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[388] ETH.MESH.00274015

[389] Jeffery S, Acharyya R, Algar M, Makhene M, Makhene M Mini-sling procedures in stress urinary incontinence: a systematic review of efficacy and complications (Abstract number 5). *Neurourology and Urodynamics 2010; 29(6):* 811- 2., and presented 8/25/10 at ICS annual meeting.

"These results demonstrate the importance of a long follow-up when a new device is evaluated in the field of urinary incontinence".

"Indications of TVT-Secur for SUI in women should be reconsidered".

2011:

Abdel-Fattah et al complete what they report to be the first metaanalysis of single incision sling data. Seventy percent of the data was represented by TVT-SECUR.

The authors, lead by a SID preceptor, noted that *the growing use of SIS was "proceeding in advance of any supporting high quality data" and "[R]CTs with long-term follow-up are crucial if we are to know the durability and long-term morbidity of our surgical interventions".*

"We recommend the initiation of an adequately powered and properly designed RCT to compare the new adjustable SIMS with SMUS with long-term follow-up and health economic analysis. Until then SIMS should be performed only within a research context"

They concluded, *"This current evidence applies only to the types of SIMS included in the meta-analysis and does not support their use in clinical practice". Seventy percent of the women in this analysis were treated with TVT-SECUR.*

Tommaselli et al reported on their systematic review of the literature (from January of 2006 to March of 2011) for the TVT-SECUR device.

> "*The results of this systematic review seems to indicate that TVT-Secur device objective cure rate does not reach 80%" and concluded, "The data from this analysis seems to suggest that TVT-Secur may have lower cure rates in comparison with retropubic and trans-obturator devices, but has limited complication rate".*

Walsh published his systematic review of the literature for twelve-month outcomes for TVT-SECUR.

> *"[T]here is concern that newer slings are being used prematurely, before sufficient evidence exists".*
>
> *"Longer-term studies and randomized comparisons with more established MUSs are required before TVT-S should be routinely used in the surgical treatment of stress urinary incontinence".*
>
> *"Until data exist to correctly assess the medium- and long-term cure rates after M-S procedures, practitioners must be careful in choosing this surgical approach over more established surgical options".*

"Thus, we cannot assume that the use of a mini-sling eliminates the risk of serious adverse outcomes, although the rate o f such events after TVT-S procedures remains unknown".

Thhe "[A]bsence of data on the number of sexually active women in individual studies precludes an accurate analysis of this complication. The incidence of dyspareunia after a TVT-Secur mini-sling procedure demands further study".

Tommaselli et al reported their 24 month retrospective review TVT-S implantation. They noted failure was more common than reported for the TVT-O procedure.[390]

"It seems that the positioning of TVT-Secur is highly variable and the standardization of the technique may not be easily achieved".

They concluded, "Since it involves procedural passages that may worsen its outcomes and since standardization is difficult, it should be limited to previously untreated patients affected by mild or moderate isolated SUI".

2011

[390] Tommaselli GA, Di Carlo C, D'Afierc A, Formisano C, Fabozzi A, Nappi C. Efficacy and safety of TVT-secure in the treatment of female stress urinary incontinence: a systematic review (Abstract number 867). Proceedingsofthe 41stAnnual Meetingofthe International Continence Society (ICS), 2011Aug 29 to Sept 2, Glasgow, Scotland. 2011.

Hinoul, Ethicon's Worldwide Director of Medical Affairs, and a group of co-investigators, completed their RCT comparing TVT-S to TVT-O. Five years after the introduction of TVT-S, Ethicon's medical director still remains unsure of the role of TVT Secur.

> *"The study failed to confirm the anticipated lower perioperative morbidity rate of TVT Secur since we noted increased blood loss, higher tape exposure and bladder injury rates, and a more common need for surgical re-intervention. Considering possible economic benefits or patient preferences, the role of TVT Secur remains to be studied*".

2012

Hota et al terminated an Ethicon sponsored prospective TVT-S trial early secondary to concerns of efficacy.

> *"Because of the significant difference noted in the primary outcome (CST) between groups at the time of this interim analysis, the study was terminated early. Given that the incidence of failure in the TVT-S group seemed significantly higher than that in the TVT-O group, we felt that patient care would be compromised by continuing the study".*

"Given the inconsistent data of the published case series and the low long-term cure rates found in this present study, we believe that more level I evidence from properly designed randomized controlled trials is needed as new surgical devices to treat stress incontinence are introduced to evaluate safety and efficacy".

Barber et al published their non-inferiority trial that failed to demonstrate non-inferiority of the TVT-S "U" method compared to TVT retropubic. Their findings of minor improvements in complications rates were confounded by increased concomitant hysterectomies amongst the TVT-S patients.[391]

"The minor improvements in complication rates and the postoperative patient experience demonstrated by TVT SECUR seem to be overshadowed by a significantly greater incontinence severity after surgery, however".

"This highlights the need for rigorous clinical trials evaluating the efficacy and safety of new innovations in treatment for SUI relative to standard retropubic or transobturator mid-urethral slings before widespread adoption".

Cornu et al (2012)[392]

[391] Barber, Matthew D., Alison C. Weidner, Andrew I. Sokol, Cindy L. Amundsen, J. Eric Jelovsek, Mickey M. Karram, Mark Ellerkmann, Charles R. Rardin, Cheryl B. Iglesia, and Marc Toglia. "Single-Incision Mini-Sling Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence." *Obstetrics & Gynecology* 119.2, Part 1 (2012): 328-37.

[392] Cornu, Jean-Nicolas, DaphnÃ© LizÃ©e, Philippe SÃ¨be, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, and FranÃ§ois Haab. "TVT SECUR Single-Incision Sling After 5 Years of Follow-Up: The Promises Made and the Promises Broken." *European Urology* 62.4 (2012): 737-38.

In 2012 Cornu et al reported on their five-year prospective observational study of 45 consecutive women undergoing implantation with the TVT-S device.[393] Mean follow-up was 59 months. Since the midterm analysis with a 30 month mean follow-up, the cure rate had decreased from 40% to 31. The authors concluded,

> *"In our experience, the TVT SECUR device definitely did not stand the test of time, with a 31% success rate after 4.5-yr of follow-up, and it should not be considered a valuable option for SUI management unless supplementary data are provided regarding its long-term outcome." One of the authors was a paid consultant of Ethicon.*

Ethicon's internal document, Background Information on the TVT SECUR.[394]

> "While the TVT-Secur product is associated with inferior patient-reported and objective cure rates at 1 year, and higher reoperation rates when compared to standard mid- urethral slings (e.g. TVT TM /TVT-O TM), Ethicon has concluded that the minimally-invasive procedure using TVT-SecurTM is an acceptable choice of therapy for a carefully selected patient population when implanted by experienced surgeon".

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[393] Cornu, Jean-Nicolas, DaphnÃ© LizÃ©e, Philippe SÃ¨be, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, and FranÃ§ois Haab. "TVT SECUR Single-Incision Sling After 5 Years of Follow-Up: The Promises Made and the Promises Broken." *European Urology* 62.4 (2012): 737-38.

[394] ETH.MESH.05600922

2014

The Cochrane Organization (Nambier et al) published its systematic review of the literature. Their narrative included:

> *"TVT-Secur is inferior to standard mid-urethral slings for the treatment of women with stress incontinence and has already been withdrawn from clinical use"*

> *"TVT-Secur is a specific type of mini-sling that has consistently been shown to provide poorer control of incontinence, along with higher rates of side effects, compared with standard mid-urethral slings".*

> *"It should be noted that TVT-Secur (Gynecare, Bridgewater, N] , USA) is one type of single-incision sling; it has been withdrawn from the market because of poor results".*

Schempf et al published their systematic review of the literature.[395] These authors reviewed fifteen randomized controlled studies comparing TVT-S to other midurethral slings (MUS). Six studies were available for assessment of objective cure.

> *"Traditional MUS are significantly superior to minislings for cure outcomes"* and *"Dyspareunia is more common with minisling than either retropubic or obturator sling, but absolute rates are low for all types of slings".*

[395] **Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211:71.e1-27.**

2016

The U.K. NICE group published their updated guidance on Single Incision Slings:[396]

> "Clinicians wishing to do single-incision short sling mesh insertion for stress urinary incontinence in women should:
>
> *"Inform the clinical governance leads in their NHS trusts".*
>
> *"Ensure that patients understand the uncertainty about the procedure's safety and efficacy, including that there is the potential for the procedure to fail and for serious long-term complications from the device, and that the mesh implant is intended to be permanent so removal, if needed, may be difficult or impossible".*
>
> *"Provide patients with clear written information. In addition, the use of NICE's information for the public is recommended. Audit and review clinical outcomes of all patients having single-incision short sling mesh insertion for stress urinary incontinence in women".*

[396] National Institute for Health and Clinical Excellence. lnterventional procedure guidance 566. Single-incision short sling mesh insertion for stress urinary incontinence in women. October 2016. NICE, London, UK. Available at: http ://www.nice.o rg.uk/guidance/IPG566

"Patient selection should be done by a multidisciplinary team with experience in the assessment and management of women with stress urinary incontinence".

Dated: **July 27th, 2017**

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